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THE ANTERIOR PITUITARY GLAND AND DIABETES MELLITUS*

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OUR knowledge of the influence of the pituitary gland on carbohydrate metabolism, unsatisfactory though it may be, has increased with remarkable rapidity during the last ten years. It will be universally agreed that the credit for the initiation of this rapid advance in our knowledge should go to Houssay and his colleagues in Buenos Aires; the important pioneer investigations of this group of workers opened up an entirely new field of research, a field that has yielded results of the greatest importance in the formulation of our present theories of carbohydrate metabolism. Striking developments have since been made in other laboratories, of which must be mentioned the investigations of Long, Lukens and their collaborators on the role of the adrenal cortex in experimental diabetes, the researches of Russell, Cori, Bennett and others on the nature of the metabolism of the hypophysectomized animals and the significant investigations of Collip, H. M. Evans, Himsworth, Soskin and others.

The numerous publications of Houssay and his collaborators have been adequately reviewed during the last few years (Houssay, 1936 and 1937) and no more will be done here than to summarize their fundamentally important initial results. These can be conveniently considered under five main headings.

(1) Experimental removal of the pituitary gland results in greatly increased sensitivity to the hypoglycemic action of insulin (Houssay and Magenta).

(2) In toads, removal of the pars glandularis of the hypophysis, as well as of the whole pituitary gland, greatly increases the sensitivity of the animal to the action of insulin. The hypersensitivity of the hypophysectomized toad to the action of insulin could be diminished by treatment with preparations from the pars glandularis of the pituitary gland, although preparations from the pars nervosa together with the pars intermedia were ineffective under similar conditions (Houssay and Potick). Similar results with respect to the importance of the anterior lobe in the control of insulin sensitivity have since been obtained with rats by other workers (Pencharz, Cori and Russell; Swann and Fitzgerald), although Geiling, Campbell and Ishikawa had previously found that in one dog extirpation of the anterior lobe of the pituitary gland was not followed by a great increase in insulin sensitivity such as follows removal of the whole gland.

(3) In toads and dogs, hypophysectomy previous to or following pancreatectomy usually diminishes the severity of the diabetic condition which results from removal of the pancreas only, in these species (Houssay and Biasotti).

(4) Treatment of hypophysectomized and depancreatized animals with anterior pituitary extracts results in a great intensification of the diabetic condition, indicating the possibility that in animals from which the pancreas alone is removed, the diabetic condition is brought to its normal degree of intensity under the influence of the secretions of the pituitary gland (Houssay and Biasotti; Houssay, 1936).

(5) The injection of suitable anterior pituitary extracts into normal animals results in the appearance of symptoms of diabetes (Houssay, Biasotti and Rietti). In this observation Houssay and his colleagues were anticipated by two other groups of workers (H. M. Evans et al., and Baumann and Marine). In the experiments of Evans and his colleagues a diabetic condition was observed in two dogs eight or nine months after daily injections of an anterior pituitary growth-promoting extract had been instituted. The animals were in a poor condition at this time and the diabetic condition did not disappear for some months after cessation of treatment, although in the experiments of Houssay and others the symptoms subsided and disap-

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peared within a few days of stopping daily injections of extract.

These observations by Houssay and others suggested, in agreement with the earlier clinical observations, that overactivity of the pituitary gland, as well as dysfunction of the islets of Langerhans of the pancreas, might be considered as a possible cause of diabetes mellitus. Houssay's results stressed the importance in carbohydrate metabolism of the anterior lobe, rather than that of the posterior portion of the pituitary gland, and although Collip has recently suggested that the

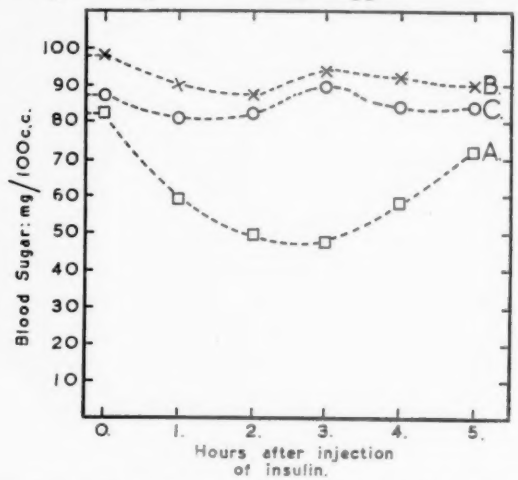

FIGURE 1. *Hypoglycemic Action of Five Units of Subcutaneously Administered Insulin in Dogs Fasting Eighteen Hours.*

Curve A: *normal dog. Curve* B: *dog which had become refractory to the diabetogenic action of an anterior pituitary extract, after an initial response. Curve* C: *dog which had not yet become diabetic as the result of treatment with anterior pituitary extract.*

secretions of the pars intermedia may be of significance in this connection, most of the results to be discussed in the present communication have been obtained with extracts of the anterior lobe. It must be admitted, however, that these extracts were contaminated with traces of the melanophore expanding principle from the pars intermedia.

THE DIABETOGENIC ACTION OF CRUDE ANTERIOR PITUITARY EXTRACT

When an animal receives one or more daily injections of anterior pituitary extract, it may sub-

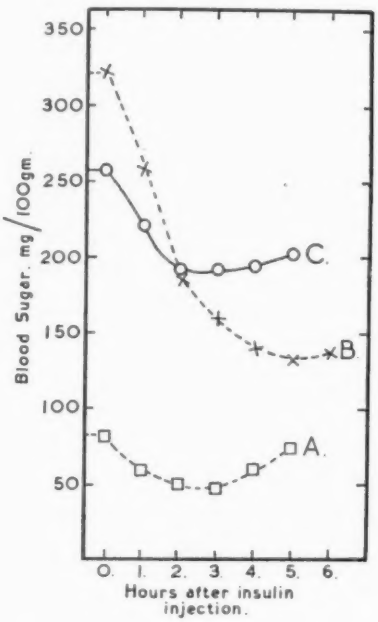

FIGURE 2. *Hypoglycemic Action of Five Units of Subcutaneously Administered Insulin in Dogs Fasting Eighteen Hours.*

Curve A: *normal dog. Curve* B: *dog made permanently diabetic by treatment with anterior pituitary extract; response determined some months after the cessation of injections. Curve* C: *dog made temporarily diabetic by treatment with anterior pituitary extract; response determined during the period of injections.*

The absolute fall of blood sugar in Curve C *is greater than that in the control curve, but the percentage fall is much less. Curve* C *therefore illustrates diminished sensitivity to the action of insulin. In Curve* B *both the absolute and the percentage fall of blood sugar level are greater than the corresponding values for the control curve. Curve* B *therefore illustrates no diminished sensitivity to the hypoglycemic action of this dose of injected insulin.*

PLATE 1. *(Histological preparations by Mr. K. C. Richardson.)*

A. *An islet of Langerhans from the pancreas of a dog which had become refractory to the diabetogenic action of an anterior lobe extract, showing a mitotic figure in a beta cell. The beta cells are partly degranulated, the alpha cells are normal. Magnification,* × *710.*

B. *An islet of Langerhans from the pancreas of a dog made temporarily diabetic by anterior lobe extract, showing advanced stages of hydropic degeneration in four islet cells. (The section has not been stained specifically to demonstrate the cell-types.) Magnification,* × *580.*

C. *An islet from the pancreas of permanently-diabetic Dog 44, consisting mainly of alpha cells with a few partly degranulated beta cells. The specimen was taken twelve months after the cessation of injections. Magnification,* × *610.*

D. *An islet from permanently-diabetic Dog 44. In the islet the beta cells are agranular and presumably in a state of exhaustion. The alpha cells have become densely crowded together. The print has been overexposed to emphasize the agranular condition of the beta cells. Magnification,* × *470.*

KEY. a: *alpha cell.* b: *beta cell.* db: *beta cell depleted of its specific-staining cytoplasmic granules.* pb: *beta cell which has lost part of its cytoplasmic granules.* h: *cell undergoing hydropic changes.* m: *mitotic figure.*

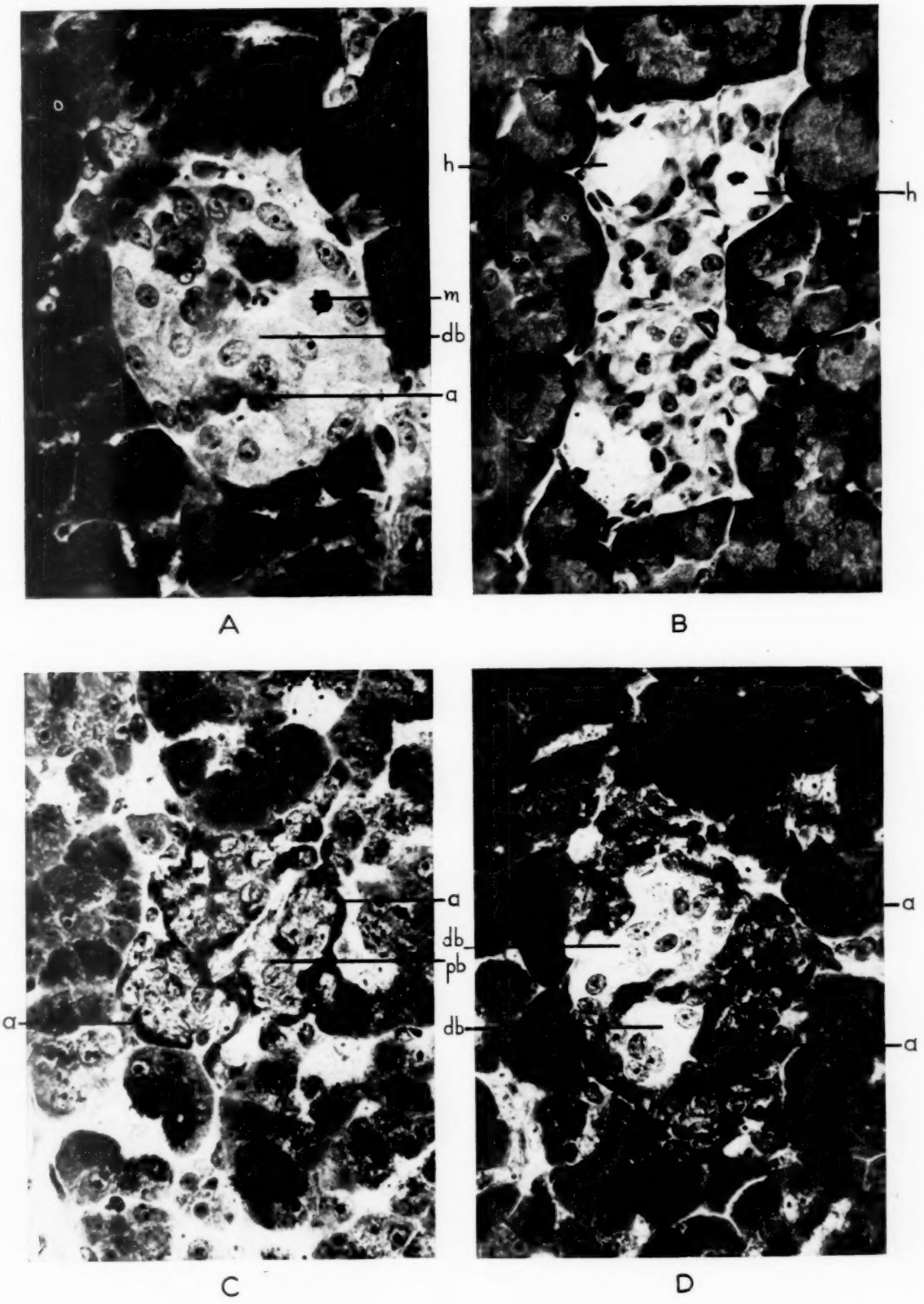

PLATE 1.

sequently exhibit insensitivity to the hypoglycemic action of a test dose of insulin, injected at the end of a short period of fasting, even though the blood-sugar level is not significantly raised by the treatment with pituitary extract (Fig. 1). If, however, daily injections of a crude extract are continued for some days, a high fasting blood-sugar level may be found, still associated with insulin insensitivity (Fig. 2) (cf. di Benedetto), which, however, is more marked in the rabbit than in the dog. There is good evidence that the anterior pituitary principle causing the rise of blood-sugar level (the diabetogenic principle) is not identical with that inducing insensitivity to the hypoglycemic action of insulin (the glycotropic principle [Young, 1936, 1938 a]).

When a dog receives daily injections of a crude anterior pituitary extract for some days, after the latent period during which the general blood-sugar level is not significantly raised although insensitivity to injected insulin develops, the blood-sugar level slowly rises and the symptoms of diabetes appear, that is, the animal exhibits hyperglycemia, glycosuria, polyuria, ketonuria, hyperlipemia and acidosis; the sugar tolerance is diminished and the administration of glucose is followed by a subnormal rise of the respiratory quotient, much of the ingested sugar being excreted in the urine. The main differences between the diabetic condition produced by treatment with anterior pituitary extract and that following removal of the pancreas are (in dogs) the relative insensitivity to the hypoglycemic action of insulin, the tendency to gain rather than lose weight and the high liver-glycogen content of the animals made diabetic by pituitary extract (confirmed in our laboratory: see also Young, 1937 b, and Marks and Young, 1938 a).

Houssay observed that the diabetic condition induced by treatment with anterior pituitary extract was greatly diminished in intensity, or entirely abolished, by fasting, and that the condition disappeared within a few days of the cessation of daily injections of extract. E. I. Evans, and later Young (1936), found that the symptoms of diabetes in the dog disappeared during the course of seven to ten days, in spite of daily treatment with the same dose of extract. Young further observed that the symptoms of diabetes reappeared if the amount of extract injected daily was suitably increased but again subsided despite the continuation of daily treatment with the increased amount of extract. A further rise in the amount of extract injected daily again resulted in a reappearance of the diabetic condition, which, as before, disappeared when the same amount of extract was administered each day for some days. It was found that this disappearance of the symptoms, followed by their reappearance with an increase in the amount of extract injected daily, could occur a number of times; it was observed in rabbits, cats and dogs, although the last-named species appeared to be the most generally satisfactory for investigations of this nature. We have observed that those animals which have become resistant to the diabetogenic action of the extract are nevertheless still relatively insensitive to the hypoglycemic action of injected insulin (Fig. 1), and that the fasting liver glycogen content is still abnormally great (cf. Young, 1937 b). For instance, Dog 72, which had become refractory to the diabetogenic action of an anterior lobe extract, but which, nevertheless, was still relatively insensitive to the hypoglycemic action of 5 units of insulin, possessed 9.9 per cent of liver glycogen and 2.25 per cent of muscle glycogen after a fast of twenty-four hours. These experiments indicate that development of refractoriness to the action of the diabetogenic principle in the pituitary extract is not necessarily accompanied by the development of resistance to its glycotropic (anti-insulin) action, nor to its action on the retention of glycogen during a short fast.

THE "PANCREATROPIC" ACTION OF ANTERIOR PITUITARY EXTRACTS

Examination of the islets of Langerhans of dogs which had developed refractoriness to the diabetogenic action of an anterior pituitary extract revealed unusual mitotic activity (Plate 1 *A*; Richardson and Young, 1938) associated with hydropic degeneration (Plate 1 *B*; cf. Allen, 1922). Sometimes these two processes were found to be proceeding simultaneously in the same islet. It should be stressed that mitoses in islet cells in the pancreas of a normal dog are so rare as almost entirely to escape observation. The unusual mitotic activity in the islets suggested the possibility that the animals had become resistant to the diabetogenic action of the extract because the islets had hypertrophied and were secreting more insulin. It was, of course, possible that the mitotic activity represented nothing more than replacement of cells which had undergone hydropic degeneration. Nevertheless, we were particularly interested in the statement by Anselmino, Herold and Hoffmann that anterior pituitary extracts possess a "pancreatropic" action. According to these workers the administration of an anterior pituitary extract to normal rats results

in a few days in a substantial increase in the number and size of the islets of Langerhans of the pancreas. They ascribe this increase to the action of a "pancreatropic substance" believed to be present in the pituitary gland. This substance was found to cause not only hyperplasia of the islets, but also an increase in the amount of insulin secreted by the islets, as shown by the fall of blood sugar occurring immediately after injection of an extract (Anselmino and Hoffmann). In the experiments of Anselmino and his colleagues the increase in the size and number of the islets was assessed solely on the basis of the histological appearance of sample sections of the pancreatic tissue from pituitary-treated animals, a method which is obviously open to objection. It is therefore not surprising that there has been much disagreement with respect to the question of this alleged pancreatropic action of pituitary extracts (for references see Richardson and Young, 1937). Richardson and Young (1937), using a tedious but objective method for the quantitative determination of the pancreatic islet tissue in the rat, found that the amount of islet tissue in the animals which had received daily injections of a crude pituitary extract for some weeks was about double that in control animals. They were, however, unable to confirm the activity of the type of extract used by Anselmino et al. under the conditions defined by the latter workers. More recently Marks and Young (1939) have found that the insulin content of the pancreas of the pituitary-treated rat may be more than twice that of control animals, suggesting that the extra islet tissue, formed as the result of the hypophyseal stimulus, is functionally active.

The physiological significance of this pancreatropic action of pituitary extracts is difficult to determine in the light of experiments by Krischesky and by Adams and Ward, demonstrating that removal of the pituitary gland may be followed by an increase in the amount of pancreatic islet tissue. Moreover, Krischesky, using a quantitative method for the assessment of islet tissue, found that treatment of hypophysectomized rats with crude anterior lobe extract depressed the rise in the amount of islet tissue in the pancreas which occurred in hypophysectomized animals in the absence of such treatment. Nevertheless, it seems proved that the treatment of normal rats with anterior pituitary extracts can increase both the amount of islet tissue and the amount of insulin found in the pancreas, and this effect will be described as a pancreatropic effect of the pituitary extracts. In the absence of a demonstration of an appropriate insufficiency syndrome, it is clearly unwise to speak of a pancreatropic hormone.

As the type of pituitary extract which was effective in increasing the amount of islet tissue and of insulin in the pancreas of the rat was also active in producing the symptoms of diabetes in dogs, it seemed possible that the islet hypertrophy was a compensatory response to the diabetic condition induced by treatment with the extract, prompter and more effective in the rat than in the dog. However, the blood-sugar levels of rats receiving daily injections of these crude extracts were within normal limits (Richardson and Young, 1937; Young, 1938 a), and although the possibility could not be entirely ruled out, it seemed improbable that the islet hypertrophy could be merely a compensatory response to the diabetogenic action of the extract.

Some noteworthy experiments by Houssay and Foglia (1936), involving the grafting of the pancreas from one dog into the neck of another, have demonstrated that the pancreas of a dog which is temporarily diabetic as the result of treatment with anterior pituitary extract is secreting less insulin than the pancreas of the normal dog. This decreased insulin secretion may result from a partial exhaustion of the power of the islets to secrete insulin, brought about by the raised blood-sugar level, or it may be due to a direct action of the pituitary extract on the islets, depressing the secretion of insulin. Whatever may be the explanation of these results, it seems reasonable to suppose that the dog is able to develop refractoriness to the diabetogenic action of a small daily dose of anterior pituitary extract, because the pancreatropic action of the extract has made more insulin available.

THE PRODUCTION OF A PERMANENTLY DIABETIC CONDITION IN THE DOG BY TREATMENT WITH ANTERIOR PITUITARY EXTRACT

As the dog was found to be capable of developing refractoriness to the diabetogenic action of the daily administration of a relatively small dose of anterior pituitary extract, it was of interest to determine whether or not such refractoriness would develop when a very large dose was injected daily for some days. With this object in view Young (1937 a; 1938 b) gradually increased the amount of extract administered daily to a dog, in such a way that the amount eventually administered each day was equivalent to 25 gm. of fresh ox anterior lobe, and found that refractoriness to the daily administration of this amount of extract was not developed. Moreover, when the daily injections of extract were stopped the diabetic condition continued and had apparently become permanent (Young, 1937 a). Later it was found that if the amount of extract administered

daily to the dog was increased after each three-day period, the development of the refractory condition could be avoided (Fig. 3), and a permanently diabetic condition thus induced more rapidly. One dog was made permanently diabetic in this manner after only eleven days' treatment with pituitary extract. Campbell and Best, Houssay, Biasotti and Dambrosi, and Dohan and Lukens have recently confirmed this observa-

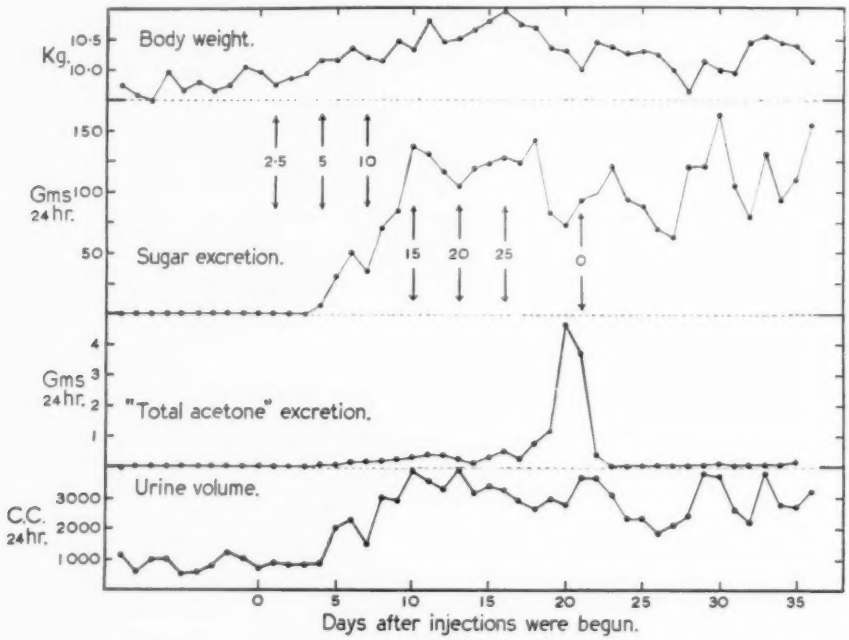

FIGURE 3. *Data Relating to Dog 44 during the Period of Establishment of the Permanent Diabetes.*

The figures on the arrows give the weight in grams of fresh ox anterior pituitary tissue used to prepare the amount of crude extract injected daily, from the day indicated by the arrow, onward. The injections ceased on the day indicated by the arrow marked "0." The ketonuria fell to a low level following the cessation of injections but rose later. (Reproduced from Proc. Roy. Soc. Med. 31:1305–1316, 1938, *by permission of The Royal Society of Medicine.)*

tion; that is, that a clearly defined and permanent diabetic condition may be produced in dogs by a short period of treatment with crude anterior pituitary extract.

In our experience a period of intense treatment is required to bring about the permanently diabetic state, and if treatment is stopped before a sufficient intensity has been reached and maintained for some days, the diabetic condition may disappear after the daily injections of pituitary extract cease. We have gained the impression that there is a definite point at which the phase of temporary diabetes resolves into a condition of permanent diabetes. According to our experience, once the permanent state has been produced it shows no sign whatever of remission, even though, as the result of treatment with insulin, glycosuria is almost completely suppressed for a long period. On the contrary, the diabetic condition tends to increase rather than to decrease in severity with the passage of time. It is convenient to consider the response of the dog to the daily administration of diabetogenic pituitary extract as divisible into a number of phases. First, the latent period, during which hyperglycemia and glycosuria are not observed, although a relative insensitivity to the hypoglycemic action of injected insulin is found. Second, the phase of temporary diabetes, during which there is still a relative insensitivity to the action of administered insulin, and the liver-glycogen level is high. Third, the refractory phase, during which the blood-sugar level is normal but insulin insensitivity persists, and a high fasting liver-glycogen level is found. The development of this refractory phase can be circumvented by rapidly increasing the amount of extract injected daily. Finally, if the amount of extract administered each day is increased to a sufficient degree, the resurgent phase of temporary diabetes may resolve into a permanently diabetic condition, which persists indefinitely after cessation of treatment with pituitary extract. When the response to insulin, of dogs thus made per-

manently diabetic, is determined some time after the injections of extract have ceased, it is found to indicate no obvious insulin insensitivity of the type found during the phase of temporary diabetes (Fig. 2), while treatment with pituitary extract is still proceeding.

There are a number of points about the transition from the temporary to the permanent condition of diabetes which may be mentioned. A symptom which we have found of use, in indicating that the permanent condition is nascent, is a rapid and substantial increase in the ketonuria (cf. Fig. 3). The excretion of ketone bodies may be only slight during the temporary phase, even though the glycosuria is intense: nevertheless, with dogs on a liberal mixed diet such as we have used, the ketonuria may suddenly increase at the time later increases, and in some of our animals we have observed a progressive increase in ketonuria over a period of a year or more. In the absence of treatment with insulin the body weight may fall slightly or remain steady for a time despite the substantial glycosuria, provided the dog is given enough protein food to cover the calories lost by the excretion of combustible material in the urine. The appetite of the animals is, of course, very large.

THE METABOLISM OF DOGS MADE PERMANENTLY DIABETIC BY TREATMENT WITH ANTERIOR PITUITARY EXTRACT

An investigation of the metabolism of dogs made permanently diabetic by treatment with anterior pituitary extract undertaken in collabora-

TABLE 1. *Insulin Requirements of Pituitary-Diabetic Dogs and of Depancreatized Dogs.**

TYPE	DOG NO.	INSULIN GIVEN	GLUCOSE EXCRETION	NITROGEN EXCRETION	CORRECTED GLUCOSE EXCRETION (N = 19.1)	GLUCOSE RETAINED PER UNIT OF INSULIN	INITIAL BODY WEIGHT	BODY WEIGHT CHANGE
		units per day	*gm. per day*	*gm. per day*	*gm. per day*	*gm.*	*kg.*	*kg. per day*
Pituitary-diabetic dog	44	60	11.0	19.4	9.9	1.9	10.8	+0.01
		50	23.7	18.7	25.1	2.0	8.9	+0.06
		20	91.8	20.8	85.7	1.9	9.8	—
	50	40	5.4	18.5	7.6	2.9	8.1	+0.08
		25	21.1	18.1	24.7	3.9	7.5	+0.06
Depancreatized dog	60	20	4.2	19.8	1.7	6.1	10.9	+0.02
	67	25	9.9	18.7	11.3	4.5	6.7	+0.03
	69	25	10.0	19.3	9.3	4.6	7.8	+0.02
	70	30	8.4	17.8	13.1	3.7	8.3	+0.03
	71	30	10.4	17.5	16.2	3.6	9.6	+0.02
Depancreatized pituitary-diabetic dog	44	30†	38.7	19.2	38.3	2.9	10.5	+0.05

*The diet consisted of 500 gm. of raw meat, 250 gm. of raw pancreas and 50 gm. of glucose daily; the figures are mean daily values for representative periods of 1 or 2 weeks.

†No glycosuria with 50 units of insulin per day.

at which we believe that the temporary evolves into the permanent diabetes; two of our dogs lapsed into what appeared to be diabetic coma at this point. The body weight tends to increase during the period of injections, but, just before the condition of permanent diabetes has apparently been established, the body weight sometimes declines to its initial value, or a little below. It appears improbable that the increase in weight during the period of injections is due entirely to growth, although some true growth probably occurs. The increase is of such magnitude in some cases as to render improbable the idea that it is due entirely to water retention, but this possibility cannot be entirely ruled out. Deposition of fat might in part account for such a rapid increase.

When the daily injections of pituitary extract are stopped, after the permanent diabetes has been established, the ketonuria may fall to a very low level, although the glycosuria continues unabated or increases in intensity. The ketonuria tion with my colleague, Mr. H. P. Marks, has revealed some interesting differences between the diabetic condition of these animals and that which follows pancreatectomy in the dog (Young, 1938 b). In particular, the amount of insulin required to regulate the glycosuria of the pituitary diabetic dog appears to be significantly greater than that required for the depancreatized dog consuming and absorbing the same amount of food (Table 1).

In order to enable a careful comparison to be made between the characteristics of the pituitary diabetic dog, which has its digestive system intact, and those of the depancreatized dog, which lacks pancreatic enzymes, we fed dogs of both types on a diet containing a large amount of raw pancreas, our diet being based on that used for depancreatized dogs by Dr. C. H. Best and his colleagues at the University of Toronto. With this diet it was possible to rectify almost completely the deficient intestinal absorption of the depancreatized dog, and to avoid the complica-

tion of fatty livers due to a deficiency of choline or other substances. Determinations of urinary and fecal nitrogen contents of depancreatized dogs receiving this diet indicated that more than 90 per cent of the protein was absorbed from the bowel. In many experiments the depancreatized dogs were given slightly more food than the pituitary diabetic dogs, in order to be certain that they were absorbing an equivalent amount of protein.

The results given in Table 1 show that the insulin required to control the glycosuria of pituitary-diabetic Dog 44 was nearly twice that required by any of the depancreatized dogs examined. On the other hand, pituitary-diabetic Dog 50 appeared to require no more insulin than did depancreatized male dogs. It should be mentioned that Dog 50 appeared, as judged by other criteria, to be somewhat less intensely diabetic than most others in our group of dogs made permanently diabetic by pituitary extracts. Although the insulin requirement of other dogs fed on the meat plus glucose diet was not accurately determined, much evidence has accumulated to show that the insulin requirement of at least two other dogs was similar to that of Dog 44, and appeared therefore to be significantly greater than that of the depancreatized dog. It is clear from these results that the severity of the permanently diabetic condition produced by treatment with anterior pituitary extract may vary substantially from dog to dog.

The results of Allan indicate that when a depancreatized dog is given different amounts of insulin while receiving the same amount of food each day, a plot of the logarithm of the number of grams of glucose retained each day, against the logarithm of the insulin dosage, should give a straight line. We have been able to confirm this both for depancreatized dogs and for our pituitary-diabetic dogs.

When Dog 44 was depancreatized, the amount of insulin required to control the glycosuria was slightly and possibly significantly diminished (Table 1). If such a diminution in insulin requirement is generally confirmed it may indicate that the acinar tissue of the pancreas plays a hitherto unsuspected role in carbohydrate metabolism. Campbell and Best have observed that, in two dogs made permanently diabetic by treatment with anterior pituitary extract, little or no aggravation of the diabetic state resulted from removal of the pancreas. However, before pancreatectomy these pituitary-diabetic dogs did not require more insulin to control their glycosuria than did ordinary depancreatized dogs, and unfortunately the result of depancreatizing another pituitary-diabetic dog, which was more resistant to insulin than any completely depancreatized dog they had ever observed, was not determined.

In spite of the large amount of insulin required to control the glycosuria of the pituitary-diabetic dogs, they are able to survive long periods without treatment with insulin, provided they are supplied with sufficient food. This is illustrated in Table 2, in which is included for comparison figures relating to a depancreatized dog which lost least weight on a meat (raw pancreas plus raw meat) diet. In our experience the depancreatized dog usually loses body weight much more rapidly than did Dog 60 during the period illustrated. It is interesting to note that the D:N ratio (corrected for the presence of small amounts of preformed carbohydrate in the meat) and the ketone excretion of Dogs 44 and 51 are both significantly higher than the corresponding values for the depancreatized dog; yet the pituitary dogs were able to maintain body weight under these conditions, whereas the depancreatized dog was not able to do so.

TABLE 2. *Data Obtained in Dogs Receiving a Meat Diet with No Insulin.**

TYPE	DOG NO.	URINE VOLUME	GLUCOSE EXCRETION	NITROGEN EXCRETION	D:N RATIO (CORRECTED)	KETONE EXCRETION	INITIAL BODY WT.	BODY WT. CHANGE
		cc. per day	*gm. per day*	*gm. per day*		*gm. per day*	*kg.*	*kg. per day*
Pituitary-diabetic dog.....	28	1550	94.8	25.7	3.40	0.70	10.2	0
	40	1450	89.2	26.9	3.09	0.28	8.3	0
	44	2950	95.5	22.6	4.00	5.01	8.8	0
	50	1600	91.0	25.0	3.45	1.80	8.2	0
	51	2750	102.9	26.6	3.69	4.03	7.2	0
Depancreatized dog.....	60	2000	91.2	23.7	3.47	2.96	8.9	− 0.07

*The figures are mean daily values for 1 or 2 weeks.

The difference in ability to survive without insulin therapy is well illustrated in Figure 4, in which are illustrated data relating to a period during which pituitary-diabetic Dog 44 and depancreatized Dog 60 were both gradually deprived of insulin under similar conditions. As the result of insulin deprivation Dog 60 rapidly lost body weight and died, although Dog 44, after an initial loss of body weight, continued to live in good condition without insulin for some

months. This was in spite of the fact that, under similar conditions, Dog 44 required about three times as much insulin as did Dog 60 in order to regulate the glycosuria. It should be emphasized, however, that if the pituitary-diabetic dogs are suddenly deprived of insulin after a period of

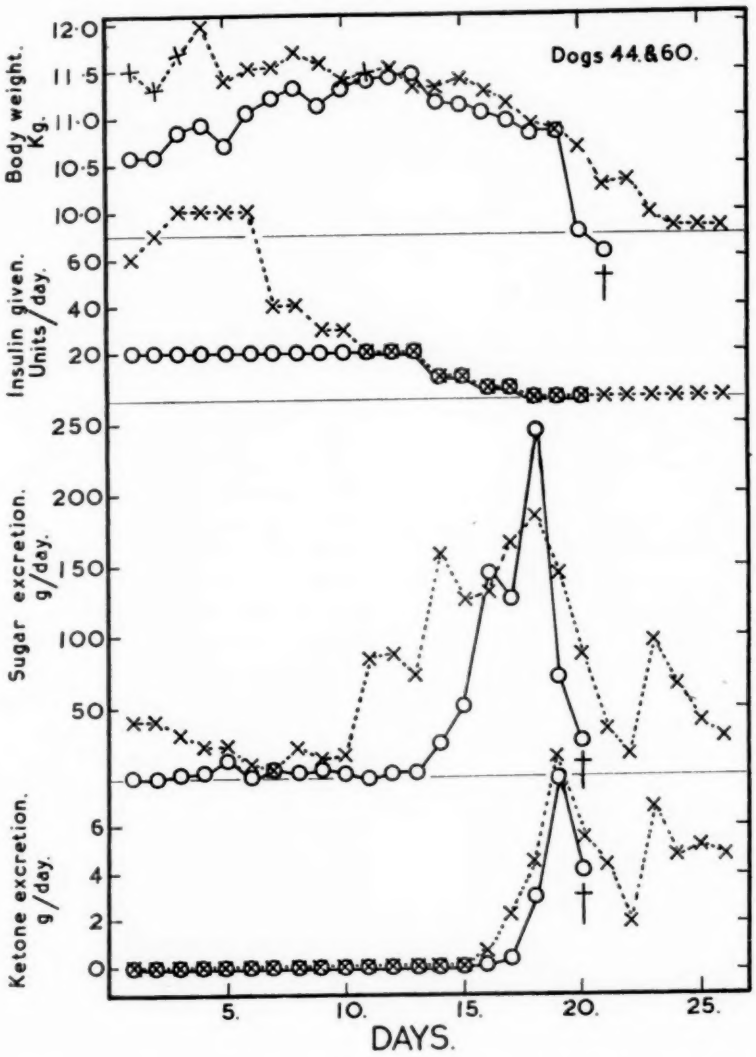

FIGURE 4. *Data Relating to Pituitary-Diabetic Dog 44 (dashed curves) and to Depancreatized Dog 60 (continuous curves) at a Time When Insulin Was Gradually Withdrawn after a Period of Experimental Therapy.*

Both dogs were receiving and absorbing the same amount of food during the period of insulin administration. Dog 60 died on the twentieth day of the period illustrated.

therapy, they may lapse into a coma which terminates fatally (cf. Young, 1937 a).

In our experience the corrected D:N ratios and ketone excretions of the pituitary-diabetic dogs vary substantially from time to time, but only with Dog 40 did the corrected D:N ratio on a meat diet fall even slightly below 3.0:1, the values for the other dogs lying between 3.4:1 and 4.0:1. The ketone excretion appeared to vary with the type of meat consumed (vide infra). As the result of a short fast the D:N ratio fell to a figure close to the classical value found by Minkowski, namely 2.8:1. At the end of a forty-eight-hour fast the blood-sugar level of our dogs averaged 250 mg. per 100 cc.

When 50 gm. of glucose was added to the food of our pituitary-diabetic dogs receiving a meat diet, nearly the whole of the extra glucose was excreted in the urine, as indicated by the relative constancy of the corrected D:N ratios. Al-

though the values varied from time to time, on the average about 90 per cent of the added glucose was found in the urine. When 50 gm. of glucose was given by mouth to a fasting pituitary-diabetic dog, the sugar-tolerance curve was of a strongly diabetic type (Fig. 5). Respiratory data obtained

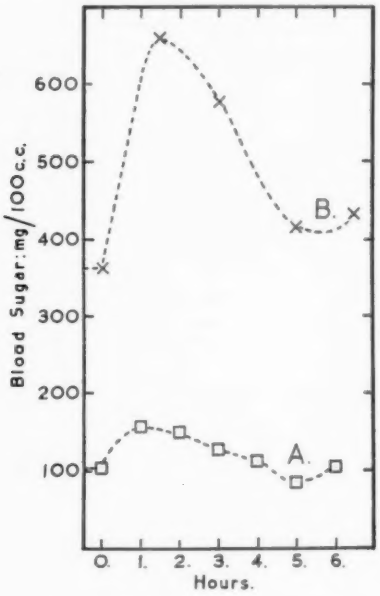

FIGURE 5. *Sugar Tolerance Curves in Dogs.*

Curve A: *average blood-sugar response of 5 normal dogs to the oral administration of 50 gm. of glucose. Curve* B: *average response of 4 pituitary-diabetic dogs to the oral administration of 50 gm. of glucose.*

by Mr. Marks showed that no significant rise of the respiratory quotient occurred as the result of the administration of 50 gm. of glucose to these dogs.

When the pituitary-diabetic dogs received a high-carbohydrate (biscuit) diet, the glycosuria was intense, although the ketonuria was less than when the animals were receiving a protein diet. On the average all the preformed carbohydrate in the diet was excreted in the urine, but when the total available carbohydrate in the diet was calculated (assuming that protein in the food was converted to sugar according to a D:N ratio of 3.6:1) it was found that only about 85 per cent of all the available carbohydrate appeared in the urine. It is therefore to be assumed that the pituitary-diabetic dogs are able to oxidize a small amount of sugar when the diet contains a high proportion of this material.

Some of our pituitary dogs tolerated a high-fat diet, consisting of beef suet only. On such a diet, glycosuria and ketonuria were both diminished (Marks and Young, 1938 b; Young, 1938 c), and in the case of one dog which tolerated the diet for some weeks, it was possible to demonstrate a substantial increase in sugar tolerance as the result of feeding this fat diet. The addition to the fat of raw meat, but not of cooked meat or casein, resulted in an increase in ketonuria (Young, 1938 c). It is difficult to reconcile these results with the classic theories regarding ketone formation from fatty acids, for it appears from our experiments that the excretion of ketone bodies by the pituitary-diabetic dog is conditioned, not by the amount of fat in the diet, but by the amount of raw meat or some extractable substance present in the raw meat.

Himsworth has divided human diabetic patients into two classes, those who are insulin-sensitive and those who are insulin-insensitive. These two classes are differentiated on the basis of the form of the sugar-tolerance curve obtained when a small dose of insulin is given subcutaneously at the same time as the patient takes a test dose of glucose by mouth. As judged by the results of a similar test carried out on Dog 44 our pituitary-diabetic dogs fall into the insulin-sensitive class.

De Wesselow and Griffiths found that the plasma from a certain type of diabetic patient resembles an extract of the anterior pituitary gland in that the administration of such plasma to a fasting rabbit results in a depression of the animal's sensitivity to the hypoglycemic action of administered insulin. We have not been able to obtain similar results with plasma from our pituitary-diabetic dogs.

THE ISLETS OF LANGERHANS OF THE PANCREAS IN PITUITARY-DIABETIC DOGS

The general sensitivity to insulin of the pituitary-diabetic dogs did not suggest that the diabetic condition of these animals persists because of continuous hypersecretory activity on the part of the anterior pituitary gland. In the circumstances it was of interest to examine the histological appearance of the endocrine glands of these animals, and in particular the islets of Langerhans of the pancreas. A careful histological examination was carried out by my colleague, Mr. K. C. Richardson (Richardson and Young, 1938), who could find no obvious changes in the thyroid, adrenal or pituitary glands of these animals. The pancreatic islets, however, showed changes which ranged from depletion of the cytoplasmic granules of the beta cells to complete replacement of islets by hyaline material. In some cases (Plate 1 *C* and *D*) the beta cells were greatly diminished in number and many islets consisted either of clumps of alpha cells only, or of alpha cells together with hyaline material. The pancreas of Dog 40 was of particular interest, as the only obvious change was a diminution

in the cytoplasmic granule content of many of the beta cells, although some islets contained beta cells with a normal content of chromophil granules. It should be emphasized that hydropic degeneration was not an obvious feature of the pancreatic islets of these permanently diabetic dogs, although, as has been mentioned already, degeneration of this type was common in the islets of dogs which were actually undergoing treatment with diabetogenic pituitary extracts. It seems possible that obvious hydropic degeneration is brought about by the strain of a sudden induction of a diabetic condition, but that, when a permanent diabetes has been established, the adjustment is such that any degeneration of the hydropic type is going on at a rate so slow as not to be obvious. Beta cells in hydropic degeneration were observed in a few islets of Dog 40 but not in any of the islets of other permanently diabetic dogs in which a careful examination was made; the paucity of beta cells in these cases may, of course, have been caused by previous hydropic changes.

Mr. Richardson reports that a constant finding in the pancreatic tissue of dogs which have been treated with anterior pituitary extracts is vacuolation of the intralobular duct epithelium. This change has been observed in pancreatic tissue from dogs which have been treated with anterior lobe extracts having no evident diabetogenic activity. If new islet cells proliferate from the epithelium of the intralobular ducts during life, as they undoubtedly do in the embryo, the observed changes in the duct epithelium may be of significance in the search for a reason to account for the lack of replacement of the degenerated islet tissue in these permanently diabetic dogs.

We have now to consider whether, in every case, the changes in the islets of Langerhans observed in our dogs are sufficient to account for their permanently diabetic condition. In most of our animals the islets were so abnormal that there is little difficulty in assigning to this change alone the persistence of the diabetic condition. In the case of Dog 40, however, the changes in the islets were of such a slender nature as to render doubtful the assumption that they alone were able to account for the permanently diabetic condition of this animal. It is true that the condition was somewhat less intense than that of the other dogs we have examined, but corrected D:N ratios of about 3.0:1 were observed when this dog was receiving a full-protein diet, and there is no reason to doubt that it was suffering from a severe permanent diabetes. Also, in the case of Dog 44, the changes in the islets are relatively slight, when the intensity of the diabetic condition of this dog is taken into account. It is therefore unwise to consider as precluded the possibility that the diabetic condition of some or all our dogs results, in some measure, from extrapancreatic factors. There is no evidence, as we have seen, that overactivity of the anterior pituitary lobe is of importance in this connection, but the possibility of there being a deficiency of precursors of insulin might conceivably be of importance. It should be mentioned, however, that belief in the sufficiency of the changes in the pancreatic islets to account for the persistence of the diabetic condition is not rendered impossible by the observation that the pituitary-diabetic dogs may require more insulin for the regulation of glycosuria than do depancreatized dogs. As has already been pointed out, this difference in insulin requirement may be due to the presence of the pancreatic-acinar tissue in the pituitary-diabetic dogs.

THE SIGNIFICANCE OF THE ANTERIOR PITUITARY GLAND IN HUMAN DIABETES

As the result of Houssay's fundamental observations the existence of a definite type of diabetes induced by overactivity of the anterior pituitary gland was recognized. This condition could be most easily differentiated from diabetes resulting from a simple deficiency of insulin by the relative insensitivity to the hypoglycemic action of injected insulin exhibited by cases of the former type (cf. di Benedetto). Thus a convincing explanation was forthcoming for the existence of those interesting cases of human diabetes mellitus in which an extreme insensitivity to the hypoglycemic action of insulin is found; in some cases of this type many hundreds or even thousands of units of insulin are required each day in order to control glycosuria, although it seems improbable that so much insulin is secreted by the normal human pancreas. Only a very small number of human diabetic patients fall into such an insulin-resistant class, however, and in the remainder of the cases the condition is presumably to be ascribed to deficiency of function in the pancreatic islets. It is to be inferred from Houssay's results that in all cases of diabetes the severity of the condition is determined by the activity of the anterior pituitary lobe, but, in the absence of demonstrable insulin-resistance or of gross insensitivity to the action of insulin, it is to be presumed that the pituitary gland is secreting no more than the normal amount of diabetogenic principle. In such cases the existence of the condition is presumed to be due primarily to dysfunction of the islets of Langerhans of the pancreas. It is true that in many cases of human diabetes no clearly defined lesions have been ob-

served in the pancreatic islets (Warren), and the changes in the islets of our pituitary-diabetic Dog 40 were so slight as to have easily escaped detection, had not the tissue been fixed immediately after removal from the animal. Clearly, the possibility that an extrapancreatic factor is involved in the maintenance of the diabetic condition in such a case must be borne in mind.

Is it possible that a case of human diabetes resulting from lesions of the pancreatic islets may be primarily of pituitary origin? We have seen how in dogs a short period of intense treatment with anterior pituitary substances can result in damage to the islets of Langerhans and the establishment of a permanently diabetic state. In these dogs there is no obvious persistent effect of the short period of treatment with pituitary extract, other than the islet lesions and the diabetic condition; although the thyroid glands are greatly stimulated as the result of the treatment with a relatively crude anterior pituitary extract, they return to a normal condition after the cessation of treatment, and, in dogs which were examined a year or so after the permanent diabetes had been established, normal thyroid glands were found. If the results of these experiments may be used for an analysis of the etiology of human diabetes, it seems possible that cases of diabetes mellitus in which no obvious indications of pituitary hyperactivity exist, and in which lesions of the islets of Langerhans of the pancreas are presumed to be the primary cause of the condition, may nevertheless have originated as the result of a short period of overactivity of the anterior pituitary gland. It is becoming clear, as the result of investigations on the action of the sex hormones, that the secretory activity of the anterior pituitary gland may vary substantially from time to time. It is conceivable that a short period of hyperactivity might result in the liberation of such excessive amounts of diabetogenic principle as to induce those irreversible changes in the islets of Langerhans which result in the establishment of a permanently diabetic condition. If this is so, then we may have to seek the primary cause of many cases of human diabetes in the anterior lobe of the pituitary gland, rather than in the islets of Langerhans of the pancreas, although defective insulin production by the pancreatic islets may be the secondary and direct cause of the condition.

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GAS-BACILLUS INFECTION OF THE ABDOMINAL WALL

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IT IS our desire in this paper to report and discuss two cases of gas-bacillus infection that followed the operation of cecostomy for cancer of the large bowel. Few if any complications of abdominal surgery are more serious in their possibilities than gas-bacillus infections of the abdominal wall. This fact and also the rarity of the condition warrant our presenting these cases, considering the literature on the subject and discussing the treatment that gave recovery to both our patients.

Those of us who had experience with the surgery of wounds in the World War recall too vividly not only the frequency of gas-bacillus infection but also its tremendous mortality. Millar,[20] for example, reported 1329 cases of gas gangrene among 25,272 surgical cases in the American Expeditionary Forces.

In civil surgery gas gangrene is seen most commonly in crushing injuries of the extremities, with or without fractures. Nevertheless, *Clostridium welchii* infection has occasionally followed nearly every type of ordinary surgical operation. Cases have been reported following appendectomy, herniotomy, colostomy, ileostomy and cholecystectomy. One of us (H. M. C.) has seen it follow a traumatic rupture of the liver.

The occurrence of *Cl. welchii* infection as a complication of cecostomy, enterostomy or colostomy, with which we are more particularly concerned, has been previously observed and reported by a number of authors. Butler[4] reports a fatal case occurring sixty-seven hours after a Witzel cecostomy for intestinal obstruction due to volvulus of the cecum. In the same paper he records a second case following operation for gangrenous appendicitis with abscess.

Butler and Rhoades[5] report 2 cases following enterostomy for small-bowel obstruction in a series of 180 cases. The first occurred forty-eight hours after enterostomy, and the patient recovered after opening of the wound and institution of serum therapy. The second case developed within twenty-four hours after enterostomy for a strangulated ventral hernia. This case terminated fatally on the eighth postoperative day.

Eckhoff[10] reports a case of subacute intestinal obstruction in a man of fifty-nine of seven days' duration, for which ileostomy was done. The patient died twenty-four hours after operation with extensive gas-bacillus infection of the abdominal wall; swabs yielded *Cl. welchii* in pure culture. A second case is reported in a woman of sixty-two with intestinal obstruction due to carcinoma of the colon. Colostomy was done and on the fifth postoperative day emphysema of the abdominal wall developed; the following day she expired. Serum was not given.

Orr[23] reports 3 fatal cases following Witzel ileostomy. The first developed on the fifth postoperative day in a case of appendiceal abscess; the second occurred on the second postoperative day in a case of strangulated hernia; and the third occurred on the seventh postoperative day for intestinal obstruction of undiscovered origin.

ETIOLOGY

Clostridium welchii (*Bacillus welchii B. aerogenes capsulatus* or *B. perfringens*[29]), as well as other anaerobes (*Cl. oedematis maligni* or *Vibrion septique, B. histolyticus* and others) are widely scattered in garden soil and earth in general. They are, in fact, ubiquitous in their distribution. Gay[13] states that Bull obtained his most toxic strain of *Cl. welchii* from the lining of an old overcoat, and Gage[11] has observed gas bacilli in wool, and is of the opinion that they are found especially in woolen goods. That they are normal inhabitants of the intestinal tract of both man and animals seems well established.

In 1898 Veillon and Zuber[29] reported finding *Cl. welchii* (*B. perfringens*) in 98 per cent of 26 cases of appendicitis. Lanz and Tavel[18] found *Cl. oedematis maligni* in 49 of 136 cases of appendicitis. Simonds[27] reports finding *Cl. welchii* in 90 per cent of normal appendices removed at autopsy, and in 100 per cent of cases if the appendix contained fecal matter. Jennings[15] found that cultures from the contents of lumens of appendices removed at operation showed *Cl. welchii* in 90 per cent. In 1938 Bower et al.[2] found *Cl. welchii* in the flora of 60 per cent of 55 cases of gangrenous appendicitis associated with spreading peritonitis. Haerem et al.[14] found *Cl. welchii* and *Escherichia coli* (*B. coli*) to be the predominating organisms recovered from the flora of closed intestinal loops in dogs.

It is generally agreed that in the absence of any pathologic disturbance of bowel function, *Cl. wel-*

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chii as a normal inhabitant of the intestine is innocuous and produces no absorbable exotoxin. What, then, are the factors which bring about the manifestation of the potentially invasive and toxic properties of these organisms, and which give rise to clinical gas-bacillus infection of the abdominal wall, with its widespread destruction of tissue and profound toxemia, which in many cases is fatal?

Williams,[31] in an excellent paper published in 1926, states that *Cl. welchii* requires for the production of toxin a slightly alkaline or neutral medium, and that in an acid medium the toxin is destroyed. When the small bowel is obstructed conditions are excellent for the proliferation of the organism and production of its toxin. Obstruction to the large bowel likewise finally results in ideal conditions for the growth of the gas bacillus. Specimens of vomitus showed *Cl. welchii* in eleven of twelve specimens taken by Williams from patients with acute intestinal obstruction, and in nineteen of twenty specimens from patients having general peritonitis. The intestinal contents in acute obstruction showed a high percentage of infection.

Given a medium suitable for the growth of *Cl. welchii,* a second factor which increases the ease of growth of anaerobic organisms is the relative anoxemia and tissue anoxia which exist in a loop of obstructed intestine. Gatch[12] and others have clearly shown that gaseous distention of the bowel causes a decrease in blood flow through the bowel wall, which is in direct proportion to the elevation of the pressure, and that when the intraluminal pressure reaches the level of the diastolic pressure it ceases almost entirely. With the stage thus set, and with a cuff of gangrenous or ischemic bowel wall turned in around the enterostomy tube, and with muscle near by which has been more or less traumatized in opening the abdomen, it is perhaps surprising that this complication does not occur with great frequency when cecostomies are performed.

Case 1. A. B., a 67-year-old man, was admitted to the hospital with a history of abdominal pain and obstipation of 9 days' duration. For 2 days prior to entry, crampy low abdominal pain had been severe and was accompanied by much rumbling and by vomiting.

Examination showed a soft, doughy distention of the abdomen, and a flat film revealed marked distention of the colon, particularly in the transverse and splenic portions. Barium enema revealed incomplete obstruction in the proximal sigmoid, suggesting torsion. The patient failed to show any sustained improvement during the period of preoperative preparation, and on the 4th day a cecostomy was done. A No. 18 catheter was inserted through a stab wound in the cecum without apparent soiling, and a cuff of bowel turned down around the tube by a double purse-string suture. Exploration at this time revealed a constricting annular carcinoma of the splenic flexure.

The patient's progress was entirely satisfactory until 6 p.m. on the first postoperative day, 29 hours after operation, when his temperature suddenly rose to 105.5°F., and his pulse to 140. He complained of abdominal discomfort, and was obviously confused and in a state of profound shock.

Examination of the wound showed a dull, coppery-red discoloration of the skin about the incision and unmistakable crepitation on palpation. The peculiar so-called mousy odor commonly associated with this type of infection was apparent. A clinical diagnosis of gas-bacillus infection of the abdominal wall was made, which was subsequently corroborated by the laboratory study of cultures. The wound was opened and hydrogen peroxide dressings were begun and continued every 2 hours. The patient was immediately given 2 ampules (60 cc.) of polyvalent gas-bacillus antitoxin — the first intramuscularly and the second intravenously. In the next 24-hour period he was transfused, and 3 ampules of gas-bacillus antitoxin were given intravenously; in the 3rd 24-hour period 4 ampules were given; on the 4th day, 3 ampules, and on the morning of the 5th day, 1 ampule. For 3 days after onset the patient continued in a profound state of shock, and at intervals was delirious and disoriented. During this period there occurred a rapid spread of the fulminating local infectious process, with extension of the coppery discoloration and crepitus out into the right flank and across the midline covering an area fully 20 by 25 cm. In the region of the wound there was widespread destruction and sloughing of skin, muscle and fascia, accompanied by profuse drainage of a grayish-black watery discharge. At the end of the 3rd day after onset it was apparent that the process was receding, but antitoxin was continued for 2 more days. The wound slowly granulated in, and the patient's general condition gradually improved.

One month after the cecostomy was done the patient was again operated on through a left rectus incision. The descending and sigmoid portions of the colon below the annular lesion of the splenic flexure were greatly distended. The dilated loop passed through an arch-like congenital opening in the mesentery of the small bowel into the right iliac fossa, and in passing through the opening it had become twisted. The volvulus was reduced, and the loop of sigmoid withdrawn through the opening in the mesentery of the small bowel. The carcinoma of the splenic flexure was resected and an end-to-side sigmoido-transverse colostomy was done with the modified Furniss clamp.[7] The patient's course was satisfactory until the 6th postoperative day, when he became somewhat apathetic, the pulse and temperature showed slight elevation to 110 and 99°F. respectively, and he complained of abdominal discomfort. Examination of the recent wound revealed signs of gas-bacillus infection of the second operative incision, which was subsequently proved by culture. Both the local and constitutional manifestations on this occasion were relatively mild in comparison with the first attack, and within 24 hours after opening the wound and the intravenous administration of 1 ampule (30 cc.) of antitoxin the process was obviously receding. The patient from this point made a satisfactory recovery.

The simultaneous occurrence in this case of a constricting annular carcinoma of the splenic flexure and a volvulus of the sigmoid is perhaps its most significant feature and the key to the explanation of the subsequent events. It constituted, in effect, virtually a closed intestinal loop which many investigators have shown to provide optimum conditions for the proliferation of *Cl. welchii.* The

ease of control of the infection in the second wound four weeks after antitoxin had been given is noteworthy.

CASE 2. K. T., a 74-year-old woman, entered the hospital April 28, 1937, with a diagnosis of carcinoma of the transverse colon. She gave a history of mild recurrent obstructive symptoms of 2 years' duration, and of increasing bowel frequency with passage of blood and mucus for 9 months.

On examination a freely movable tumor mass the size of a grapefruit was palpable in the left lower quadrant. A barium enema showed this to be an obstructing carcinoma of the transverse colon. After 6 days of preparation with magnesium sulfate by mouth and enemas and transfusion, exploration was done. An operable carcinoma of the transverse colon was found. It was resected and an end-to-end anastomosis was done with the modified Furniss clamp.[7] A purse-string type of cecostomy was done, the cecostomy tube being brought out through the omentum and through a stab wound in the right lower quadrant.

The patient's convalescence was entirely without incident until the 7th postoperative day, when the temperature rose to 102°F., and the pulse to 115. Examination of the wound showed slight edema and reddish discoloration around the cecostomy wound. At this time crepitation was not observed. By the following morning the discoloration had extended out into the flank, and had taken on the coppery-red color characteristic of *Cl. welchii* infection. Definite crepitus, which could be heard with a stethoscope, was present in the tissues all about the incision.

The wound was opened up, with the consequent release of a large amount of grayish-black, watery discharge carrying the pungent odor commonly associated with anaerobic infection. Peroxide irrigations and dressings were begun and 1 ampule (30 cc.) of gas-bacillus antitoxin was given intravenously. This dose was repeated on the 2nd and 3rd days. The infection slowly advanced into the flank, and on the 4th day a counter-incision was made in the flank, and a copious amount of the same grayish-black, watery discharge and necrotic fragments of fascia were discharged. The dosage of antitoxin was increased to 2 ampules, given intravenously, and this amount was administered on the 5th and 6th days. At this time it became apparent that the infection was controlled. The patient showed continuous improvement and was out of bed on the 20th postoperative day, and was discharged home on the 25th day.

The report on the culture in this case was somewhat equivocal, being "morphologically compatible with *Cl. welchii*, but not diagnostic." Nevertheless the clinical features of the disease, while not so fulminant as in our first case, were so clear-cut and definite that we have no doubt whatever that it represented a gas-bacillus infection of the abdominal wall. Unfortunately, animal inoculation was not done.

DIAGNOSIS

The successful treatment of gas-bacillus infection is dependent, perhaps to a greater extent than in infection caused by any other pathogen, on early recognition and immediate institution of remedial measures. The rarity with which this type of infection occurs as a complication of abdominal surgery may lead to confusion and failure to establish the diagnosis. This delay may be fatal.

The diagnosis in the fulminating type of infection represented by Case 1 is usually made without difficulty. The process develops with lightning-like rapidity, and usually occurs within twenty-four to thirty-six hours after operation. The pulse and temperature rise abruptly, and the patient is in a state of severe shock, which appears out of proportion to the local findings. There is generally delirium of varying degree, which may be intermittent. There is severe pain referred to the wound. The local findings, the coppery-red discoloration of the skin, the crepitation and the marked tenderness on palpation are classic and hardly require repetition. Before these signs are fully developed the characteristic odor may not be observed. It is sometimes made apparent by probing the wound, which releases a small amount of grayish-black, thin, watery discharge, with or without air bubbles. Perhaps the earliest and most helpful diagnostic sign is the crepitation, which can be heard with a stethoscope as one's fingers press the abdomen near it.

In the less fulminating type of infection, represented by the second attack in Case 1 and by Case 2, the diagnosis may be more difficult to establish. The onset is usually delayed, occurring about the sixth or seventh postoperative day. The toxemia is less profound, the pulse rate rises only to 110 or 120, and the temperature to 102°F. or less. Local pain is less, or may be absent, and the characteristic signs of the infection are slower in developing.

TREATMENT

Certainly, if one is at all suspicious of gas-bacillus infection, immediate smears and cultures from the wound should be made. It is quite likely that *Cl. welchii* will be found far more frequently than one expects if more such cultures are made. While waiting for culture reports, however, active treatment should be instituted at once in any patient who is suspected of having gas-bacillus infection.

The radical methods of treatment so helpful in gas-bacillus infection of the extremities cannot be applied when the infection involves the structures of the abdominal wall. The wound, however, must be widely and freely opened by removing the skin and fascial sutures. In each of our cases only the peritoneal suture line was left intact after we had opened the wounds. Wet

dressings with hydrogen peroxide may be applied to the wounds and should be kept saturated with this solution. It seemed to us illogical to pack any gauze into the wounds. It appeared hopeless to make numerous counter-incisions, since the infection rapidly spreads through subcutaneous tissue, and we did not do this unless an abscess appeared.

In each of our cases we relied almost entirely on the use of large amounts of polyvalent gas-bacillus antitoxin with excellent results. In early 1937 sulfanilamide had not been proved beneficial in gas-bacillus infection, and we did not use it. We should use it today, but we should be very hesitant to omit giving the antitoxin as well. Macey[19] reports a case of gas-bacillus infection which could not be controlled by sulfanilamide therapy alone but was controlled with a combination of gas-bacillus antitoxin and sulfanilamide.

Chief reliance must still be placed on early and energetic use of polyvalent antitoxin, together with wide opening of the incision, debridement of necrotic fascia and muscle and irrigation of the wound with hydrogen peroxide.

In the fulminating type of infection the dose of antitoxin, which we prefer to give intravenously, should be from 3 to 4 ampules (90 to 120 cc.) daily until the infection is obviously controlled. It may be necessary to continue treatment for seven days or longer.

In the milder type of case, the dosage of antitoxin may be somewhat less — 2 to 3 ampules (60 to 90 cc.) daily. In Case 2, although the ultimate outcome was entirely satisfactory, we believe that the period of morbidity would have been shortened had we given antitoxin in larger dosage during the first three days.

X-ray therapy as an adjuvant form of treatment has been advocated by Kelly[16] and others, and Kelly suggests that benefit obtained from this form of treatment may be due to the formation of hydrogen peroxide in the tissues. He reports a series of 40 cases with a mortality of 17 per cent, which is in sharp contrast with the general mortality for this disease, in the neighborhood of 50 per cent. However, all but 2 of his cases received serum as well as x-ray treatment. On the other hand, Coleman and Bennett[8] report 14 cases treated by x-ray alone with a mortality of 72 per cent. Probably nothing is to be lost by the use of x-ray treatment along with other measures, but expected benefit from it must not lead us into the error of any relaxation of the energy with which the more orthodox measures are used. Adequate surgical drainage, debridement and intensive use of polyvalent antitoxin still constitute the basic treatment for this disease, to which with our present knowledge we should no doubt add the use of sulfanilamide.

SUMMARY

Gas-bacillus infection of the abdominal wall is an uncommon complication of abdominal surgery, which, however, may occur after virtually any type of abdominal operative procedure. It is seen most often as a complication of operation for gangrenous appendicitis, and is not rare after decompressing operative procedures for acute intestinal obstruction.

The causative organisms, *Cl. welchii, Cl. oedematis maligni* and other closely related anaerobes, are widely distributed in nature and are normal inhabitants of the gastrointestinal tract of man and animals.

Under ordinary conditions these organisms, as normal inhabitants of the bowel, are innocuous and produce no absorbable exotoxin. Under obstructive conditions of the bowel the environment becomes favorable for their rapid growth and for the release of their latent toxic and invasive properties.

Two cases are reported of gas-bacillus infection of the abdominal wall complicating cecostomy done for obstructing carcinoma of the colon, with survival in each case after treatment with polyvalent gas-bacillus antitoxin. We believe that the therapy of gas-bacillus infections of the abdominal wall should today consist of free surgical drainage, antitoxin treatment and the use of sulfanilamide.

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PRIMARY STREPTOCOCCAL PERITONITIS*

Report of a Case Which Developed While the Patient Was Undergoing Sulfanilamide Therapy

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THERE has been considerable variation in the treatment of primary§ peritonitis in children, and there has been in most instances a uniformly high mortality. We[1] recently reported an effective method of treatment of primary peritonitis as shown by a definitely lowered mortality. In that report, early operation for diagnosis of the offending organism and drainage with minimal manipulation was stressed. Specific therapy with sulfanilamide, or sulfapyridine and antipneumococcus serums, should then be started as soon as possible.[1, 2] It is the purpose of this report to reemphasize the present method of treatment of primary peritonitis, and to present the information gained from an unusual case of primary streptococcal peritonitis.

REPORT OF CASE

E. G., a white boy, aged 9 years, entered the Medical Service of the Children's Hospital, Boston, March 15, 1939, complaining of a painful swelling in the neck of 6 days' duration. Twenty-two days before entry the patient's right ear was painful and spontaneously began to discharge thin yellow pus, which continued until 6 days before entry. At this time, the left side of the neck became swollen and tender. This was associated with daily shaking chills and fever. Three days before entry, he began to vomit everything given by mouth.

There was no family history of tuberculosis, syphilis, diabetes or blood diseases. The patient's health had always been good except for whooping cough at the age of 4.

On physical examination the patient was a well-developed, thin boy who appeared acutely ill. The anterior cervical nodes on the left were moderately enlarged, indurated and tender. There was no other adenopathy. Examination of the throat was not remarkable. The left eardrum was dull gray and the landmarks were obliterated. The right eardrum was tense and bulging posteriorly. There was tenderness over the left mastoid. The heart and lungs were normal. The abdomen was not tender, and there were no masses or spasm. Rectal examination was normal. The rectal temperature was 100.4°F., and the pulse 72.

Examination of the blood showed a red-cell count of 3,280,000 with 70 per cent hemoglobin (Sahli), and a white-cell count of 25,400 with 95 per cent polymorphonuclears, 5 per cent lymphocytes and 2 per cent large monocytes. The urine contained a large trace of albumin and 20 to 30 red-blood cells and 3 to 4 granular casts per high-power field. The serum nonprotein nitrogen was 133 mg. per 100 cc., and the serum protein 5.9 gm. The throat culture grew many hemolytic streptococci. When he was admitted to the hospital, he gave the impression of bilateral otitis media, bilateral mastoiditis and acute hemorrhagic nephritis.

Sulfanilamide, 1½ gr. per pound, was started the same day. The day of entry, roentgenograms of the mastoids revealed bone destruction on the right. Paracentesis of the right eardrum was performed the day of entry with the release of a small amount of bloody fluid. On March 18, 2 days after entry, the blood level of sulfanilamide was 15 mg. per 100 cc. The patient's temperature was normal, and he seemed improved until March 19, when he complained of generalized abdominal pain for the first time and his temperature rose to 101°F. Eighteen hours after the onset of the abdominal pain, a diagnosis of generalized peritonitis was made. Incision and drainage of the peritoneal cavity was then performed under local anesthesia. A large amount of thin, greenish pus was obtained from which a beta-hemolytic streptococcus was cultured. A large amount of pus drained from the abdomen for 7 days following operation. The patient's temperature continued to be elevated between 101 and 102°F. daily. On March 22 a right mastoidectomy was performed, but the culture of the pus obtained did not grow any organisms. The blood level of sulfanilamide varied between 26 and 10 mg. per 100 cc. until March 30. During this time the serum nonprotein nitrogen decreased to 29 mg. per 100 cc., and there were fewer red blood cells in the urine. Nine days after the abdominal operation, the drain was removed and the wound healed in the next 3 days. The mastoid wound was healed 10 days after operation. The nodes in the neck had subsided by this time.

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§By primary peritonitis (also known as idiopathic or metastatic peritonitis) we mean peritonitis that is not secondary to an inflamed or ruptured abdominal viscus. The offending organism in children is most commonly a hemolytic streptococcus or pneumococcus.

On March 23 physical examination revealed signs of pneumonia at the left base. This was confirmed by a roentgenogram of the chest. A blood culture taken on March 20 was positive for hemolytic streptococcus, but several subsequent blood cultures were negative for the same organism. The red-cell count fell to 2,780,000 and numerous blood transfusions were given during his hospital course. The white-cell count remained elevated between 25,000 and 50,000.

Signs of fluid gradually appeared in the left chest, and on April 11, a blood culture was positive for *Staphylococcus aureus*. On April 13 resection of a portion of the 8th rib on the left was performed. A large amount of pus was obtained from which a beta-hemolytic streptococcus and *Staphylococcus aureus* were cultured. Sulfanilamide therapy was started again on April 4 and discontinued on April 13. The blood level of sulfanilamide during this period varied between 8.0 and 13.5 mg. per 100 cc.

After the rib resection, the patient's temperature started a downward trend, but 5 days later it again started to spike between 101 and 104°F. daily. On April 23 the left chest was re-explored, with release of more pus, from which a hemolytic streptococcus was cultured. Roentgenograms of the chest showed the heart to be markedly displaced to the right at this time. The patient's course continued to be stormy and he became very edematous. The serum protein was 4.5 gm. per 100 cc. on May 1. On May 2 two pericardial taps were performed and a total of 700 cc. of pus was obtained, from which a hemolytic streptococcus was cultured. On May 3 a pericardiostomy was performed under local anesthesia and about 1000 cc. of streptococcal pus was drained. The patient's condition improved slightly after this but soon became worse, and death followed 18 hours after the pericardiostomy. Shortly before death, aspiration of the right chest produced 650 cc. of thin streptococcal pus. Roentgenograms taken several hours previously had shown no evidence of fluid in the right chest.

Autopsy. An autopsy was performed 8 hours postmortem. The anatomical diagnoses were hemolytic streptococcus septicemia, bilateral hemolytic streptococcus pleuritis, hemolytic streptococcus pericarditis, bilateral bronchopneumonia, generalized lymphadenopathy and peritonitis (healed). There were numerous filmy fibrous adhesions between loops of intestine. There was a small localized abscess (5 cc.) in the right lower quadrant, which was sterile on culture. The appendix showed no evidence of inflammation. It was the impression at the time of performing the autopsy, 45 days after drainage of the peritoneal cavity, that the peritonitis was healed.

There are several significant points about the foregoing case. The patient entered the hospital with manifestations of a streptococcal infection which was confirmed by positive throat cultures. Sulfanilamide therapy was started immediately. The blood level of the drug was 7.8 mg. per 100 cc. on the second day, 9.8 mg. on the third and 14.9 mg. on the fourth. The patient seemed somewhat better and his temperature was normal; despite the clinical improvement and the four days of sulfanilamide therapy, the patient developed signs of generalized peritonitis. Recurrence of spread of streptococcal infection does occur when the dosage of sulfanilamide is stopped or diminished,[3] but is unusual when the drug is at an optimum blood level,[4] as in this case.

The problem then arose: Should the sulfanilamide therapy be continued alone or should it be reinforced by incision and drainage of the peritoneal cavity? The latter course was decided on, and within eighteen hours after the onset of the symptoms of peritonitis, a small incision was made under local anesthesia in the right lower quadrant. A large amount of thin greenish pus containing flecks of fibrin was released and a pure culture of a beta-hemolytic streptococcus was obtained. The wound drained a large amount of pus for about seven days. We fully realize that it is impossible to drain the entire peritoneal cavity, but this case and others[1] have demonstrated that drainage does remove considerable amounts of pus. After the operation, the dosage of sulfanilamide was increased so that the blood level was 22.3 mg. per 100 cc. the day after operation. The signs of peritonitis gradually subsided so that by nine days after operation the abdomen was negative to physical examination. The drain was removed on that day, and the wound rapidly healed.

The right mastoid was operated on three days after the peritoneum was drained; no organisms were recovered. The patient's nephritis improved, as judged by the lowered serum nonprotein-nitrogen levels. However, pneumonia developed in the lung and was complicated by empyema, from which both *Staphylococcus aureus* and a beta-hemolytic streptococcus were obtained on culture. Sulfanilamide therapy was stopped fifteen days after entry because despite high blood levels the infection was not under control. The empyema was drained, and then the patient developed a hemolytic streptococcus pericarditis. This was also drained but the patient died the same day, which was fifty days after entry.

Examination of the peritoneal cavity at autopsy revealed no evidence of active peritonitis. There were numerous adhesions and one pocket containing a small amount of sterile exudate. From a clinical and anatomical viewpoint, the peritonitis was healed. The pericardial and pleural cavities revealed evidence of widespread infection. No unrecognized focus of infection was found.

The outstanding feature of this case is that the whole train of disease processes due to a beta-hemolytic streptococcus developed while the patient was receiving large amounts of sulfanilamide. The peritonitis responded to treatment very well, and despite the pulmonary and pericardial complications, this fact is further favorable evidence that primary peritonitis due to the streptococcus should be treated by early operation so as to identify the offending organism and drain the peritoneal cavity. Sulfanilamide therapy

should be started as soon as the organism obtained at operation can be identified as a streptococcus by smear and culture.

SUMMARY

A case of primary streptococcal peritonitis, which developed while the patient was undergoing sulfanilamide therapy, is reported.

Early drainage of the peritoneal cavity is reemphasized as an important aid in the treatment of streptococcal peritonitis.

Sulfanilamide is a valuable therapeutic agent but does not always prevent spread of infection even with optimum blood levels, and other methods of treatment should not be discarded for sulfanilamide alone.

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LABORATORY DIAGNOSIS OF ENCEPHALITIS DUE TO THE EQUINE VIRUS*

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BEGINNING early in August, 1938, cases of encephalitis began to occur in southeastern Massachusetts which have been proved to be due to a virus[1, 2] which had not heretofore been known to cause disease in man. The new etiologic agent is the Eastern virus of equine encephalomyelitis, which, beginning in 1934, was recognized as the cause of disease in horses in several states along the Atlantic seaboard.

RÉSUMÉ OF CASES IN 1938

During the late summer and fall of 1938, over 50 cases of illness, suspected to be due to this virus, came under investigation by this department. Some of these cases have been proved to be caused by other etiologic agents, but in 34 cases there is reason to believe that the equine virus was the cause of the illness. Nineteen of the patients were under five years of age, and 5 were under ten. This high incidence in the younger years of life is in direct contrast to the St. Louis outbreak of encephalitis, in which those in the older age groups were most frequently attacked.

Of the 34 cases, the equine virus was isolated from the brain tissue of 9 fatal cases. Neutralizing antibodies for the virus were found in the blood of 10 cases in which the patients survived. The diagnosis has therefore been definitely proved in 19 cases. The etiology of the remaining cases is not so well established. In 9 fatal cases the pathologic picture was so characteristic that there is reason to believe that these cases were due to the same etiologic agent. In 6 additional fatal cases the clinical picture was sufficiently similar to that seen in the proved cases as to indicate the same causative agent.

At the same time that the human cases were being discovered, an epidemic among horses was present in the same area. By the end of the season nearly 300 deaths among horses, reported to have been due to encephalomyelitis, were brought to the attention of the Massachusetts Division of Livestock Disease Control. The highest incidence in human beings occurred early in September, approximately a week after the highest incidence among horses. Further information in regard to the outbreak will be found in a report[3] presented to the American Public Health Association in October, 1938. Encephalitis in human subjects due to equine virus has already been discovered in three other states. Undoubtedly cases will eventually be discovered in the other states in which the disease is prevalent among horses.

MOSQUITO TRANSMISSION OF DISEASE

Laboratory and epidemiological evidence points to the fact that the virus is transmitted by mosquitoes. As early as 1933 Kelser[4] demonstrated that mosquitoes could transmit the disease from guinea pig to guinea pig in the laboratory, and since that time it has also been transferred to horses by the bite of certain mosquitoes. Until recently it was supposed that the disease was limited largely to horses, but it now appears that the virus is probably harbored by other animals, including certain birds,[5, 6] such as pigeons and pheasants. The present opinion is that these other animals are the primary reservoir and that man and horse are merely secondary hosts which ac-

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cidentally become infected by mosquitoes which have previously bitten the animals harboring the virus.

Because it seems quite clear that the disease is carried by mosquitoes, prevention of the spread of the disease by eliminating the varieties of mosquitoes which can carry the virus seems to be the most hopeful method of control. So far only mosquitoes belonging to one family (Aedes) have been able to act as the biological host of the virus. In all other varieties the virus promptly dies in the intestinal tract of the mosquito and cannot be obtained after two or three days have elapsed following the feeding upon an infected animal. This would indicate that control measures could be limited to particular varieties of mosquitoes. Of the members of this family which have so far been incriminated, the following have been reported to be present in Massachusetts: *Aedes sollicitans, Aedes cantator, Aedes vexans, Aedes taeniorhynchus* and *Aedes dorsalis.*

MOSQUITO SURVEY OF MASSACHUSETTS

If we can profit by the experience gained in the control of malaria and yellow fever, it is believed that much more can be accomplished by directing control measures against the worst-offending varieties instead of against the whole mosquito population. To carry out such selective control, it is necessary to know where the Aedes mosquitoes are breeding. This information is being obtained in a mosquito survey sponsored by the department during the present season. More than one hundred field workers furnished by the Works Progress Administration are collecting specimens in all parts of the State. In addition, numbers of volunteer collectors have been enlisted who will obtain specimens around their own homes.

LABORATORY CONFIRMATION OF DIAGNOSIS

The only way in which a diagnosis of encephalitis due to the equine virus can be made is by laboratory procedures. Clinically the disease is the same as any other encephalitis except that it tends to be more fulminating, has a shorter course and is characterized by a high fatality rate. One helpful point is the fact that early in the disease the cell count in the spinal fluid is not especially high (usually 200 to 1000 cells per cubic millimeter) with a preponderance of polymorphonuclear leukocytes during the first two or three days of the disease, but with a rapid reversion to a preponderance of mononuclear cells as the count later decreases.

Unfortunately, an etiologic diagnosis is not possible during the first four or five days of the illness, because at that time the virus is inaccessible, as it is present only in the brain tissue, and neutralizing antibodies for the virus have not yet appeared in the blood stream. It has not yet been demonstrated how early these antibodies appear in the blood. Therefore, a 10-cc. sample of blood should be obtained as soon as a diagnosis of an encephalitis not clearly due to some other agent is made. It may eventually be discovered that neutralizing antibodies are present well before the end of the first week of illness. Since the virus is not found in the spinal fluid after the onset of symptoms, specimens of spinal fluid should not be sent in for virus examination.

From the public-health point of view it is important to establish an etiologic diagnosis, since the institution of control measures will begin as soon as a case has been discovered.

SPECIMENS TO BE OBTAINED

Since death often occurs within twenty-four to forty-eight hours after the case is first seen by the physician, the only way by which an etiologic diagnosis can be made on fatal cases is to isolate the virus from brain tissue removed post mortem. For virus isolation, the tissue must be placed in a neutral solution of 50 per cent glycerin made up in physiological salt solution. This solution will preserve the virus until it reaches the laboratory. Such a specimen should be mailed or sent by messenger to the Department of Bacteriology at the Harvard Medical School.

Further important information can be obtained by examining microscopic sections of the brain and cord. Pathologists connected with local hospitals are usually prepared to make such sections, but if such facilities are not available, the brain and cord should be preserved in 10 per cent formalin and sent to this department.

If the local pathologist has not had an opportunity to study microscopic sections of fatal cases of this disease, the department can make arrangements for him to see the material which has been accumulated in the pathological departments of the three large medical schools in Boston. In addition, the department has requested Dr. Sidney Farber, of the Children's Hospital and the Harvard Medical School, Dr. Charles F. Branch of the Massachusetts Memorial Hospitals and Boston University and Dr. Harold E. MacMahon of Tufts College Medical School to act as a committee of consultants. They have agreed to lend assistance to the pathologists of the State in examining any material which may be suspected of being from a case of encephalitis due to the equine virus.

Where the patient survives as long as four or five days, or where complete recovery takes place, a 10-cc. sample of blood taken under aseptic precautions and put into a sterile tube should be mailed or sent by messenger, with accompanying information in regard to the case, to Dr. Leroy D. Fothergill at the Department of Bacteriology of the Harvard Medical School, where examination for neutralizing antibodies will be made. When a sample has been obtained early in the disease, another sample should be obtained during the ensuing week, unless some other diagnosis has been made in the meanwhile, in order to make sure that at least one sample will be taken at a time when neutralizing antibodies can be expected to be at a high titer. As noted above, the virus cannot be isolated from spinal fluid and such specimens should not be sent in for this purpose.

The department has made arrangements to take care of the examination of specimens from any cases in which a presumptive diagnosis of encephalitis is made, but if specimens come in from a wide variety of cases in which such a diagnosis has not as yet been made it may result in more specimens' being received than can be examined, since the procedures are both expensive and time-consuming. The co-operation of physicians is therefore requested in limiting specimens to those cases in which a presumptive diagnosis of infectious encephalitis is made. It is not believed that a case which does not show a rise in temperature to at least 102°F. can be due to the equine virus. In addition to the fever, there should be distinct signs of cerebral irritation, such as the presence of spasmodic contractions or actual convulsions or of marked stupor or coma.

State House.

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REPORT ON MEDICAL PROGRESS

CONTAGIOUS DISEASES

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SCARLET FEVER

SCARLET FEVER is a disease caused by a group of beta-hemolytic streptococci capable of producing a soluble toxin. Only those individuals who are susceptible to the toxin react to this infection with a rash, the non-susceptibles showing only sore throat and fever. Most children are susceptible to the toxin. Therefore, in them the infection usually produces a rash. One attack of the disease usually affords a lifelong active immunity but such immunity is confined to this particular group of toxin-producing streptococci and not to other streptococcal diseases. Relapses are thought to be due to reinfection with another strain before a polyvalent immunity to all scarlet fever strains has been established.

Hospitalization by municipal decree of all cases of scarlet fever for four weeks has not controlled the incidence of the disease in Stockholm, but this has been accompanied by a lowering of the mortality rate.[1] Reduction of the isolation period of uncomplicated cases from four weeks to three has proved satisfactory in certain localities in the United States. In fact, it has been found safe to release adults in the summer months at the end of two weeks. Any suppurative process in the nose, ear or a wound contraindicates such release unless the absence of scarlet fever streptococci can be proved by cultures and skin tests on Dick-positive individuals. Such service can only be obtained in certain laboratories. Release cultures in uncomplicated cases have proved of no value, as return cases are just as apt to occur from those with negative as from those with positive cultures.[2] Finally, Bergen in Norway and Aberdeen in Scotland have gone so far as to remove simple scarlet fever from all legal restrictions, leaving it to the attending physician to report the case and handle it as a case of erysipelas is handled in Massachusetts. There is something to be

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said in favor of all these methods, and the results are being watched with great interest.

The treatment of scarlet fever has been greatly advanced through the use of convalescent serum[3] and the Dick antitoxin. Either of these, administered intramuscularly or intravenously within the first two days of the onset of the rash in adequate dosage, according to the age of the patient and the severity of the disease, will usually blanch the rash, reduce the sore throat and cause an abrupt fall of the temperature. Incidentally, the incidence of suppurative complications will be somewhat reduced in proportion to how early the serum is given.[4] Convalescent serum rarely gives rise to serum reactions, and the new concentrated and refined antitoxin has reduced the incidence and severity of horse-serum sickness. Serum treatment is unnecessary in mild cases and ineffective in the complications.

Sulfanilamide given in the usual dosage during the initial fever period does not reduce or shorten the fever, nor does it reduce the incidence of subsequent complications.[5] If given over a longer period it appears to reduce the incidence of complications, but clinical experiments in this longer method have not been carried out with the same care in the way of controls as were the earlier series in which the drug was used only during the fever. Furthermore, the longer the drug is used, the greater is the danger of its untoward effects. Usually these can be controlled by the discontinuance of the drug, but sudden severe anemia requires transfusion. Until a fair balance sheet is produced in regard to the beneficial protective action of this drug given as a routine over the longer period with the ill effects carefully weighed, it would seem best to recall that the early routine use of antitoxin in this disease resulted in more days of illness as a result of serum sickness than would have occurred without such treatment.

The great value of sulfanilamide in scarlet fever lies in its effect on two highly fatal complications, namely bacteremia and meningitis. In these two conditions this drug has greatly reduced the mortality and as such has materially reduced the mortality of scarlet fever, because, in New England deaths in this disease are largely due to one or the other of these two causes.

The advisability of removing badly diseased tonsils after the third week appears to have gained favor, in spite of all theoretical reasons to the contrary. The diet in scarlet fever should be the same as in any other febrile condition, and after the fever is past the diet should be the same as that for any normal individual, according to age. Nephritis is no longer considered to be the result of improper diet but of by-products elaborated by the streptococcus.

Scarlet fever can be controlled by active immunization with the toxin.[6] This has been repeatedly proved by the immunization of pupil nurses before they go on duty on scarlet fever wards. The immunity conferred is comparable to that afforded by an attack of scarlet fever. Apparently this does not result in an increase in carriers. Children can be protected in the same way.[7] This procedure has fallen into disrepute because of the large doses recommended in the past by the holders of the Dick patent, and inscribed on the commercial packages at their direction. Fortunately, the patent is soon due to expire, which will be a boon to investigative work in this disease. The administration of three doses of the "toxoid" supplied by the Massachusetts Department of Public Health has produced little or no ill effects and also a relatively low grade of immunity.[8] Until the antigenic quality of this product is improved it is not to be recommended. However, such improvement is unlikely while the Dick patent is in force.[9]

DIPHTHERIA

In recent years there has been a wave of severe diphtheria in parts of Europe, England and South America, and in these outbreaks approximately 10 per cent of the cases have been of the malignant type. From a bacteriological standpoint these severe cases are largely due to a highly pathogenic strain, endowed with the property of rapid penetration into the tissues and of producing a relatively large amount of toxin. From a practical point of view these cases present the same clinical problem as an ordinary or weakly pathogenic strain in a highly susceptible individual. Indeed, a strain of high pathogenicity is not always associated with clinical severity.[10] Consequently, it is best to use the term "malignant" in the clinical sense for any highly toxic case of diphtheria. Furthermore, it is well to bear in mind that the usual antitoxin is capable of neutralizing the toxin of both strains.

The Manzulla test for diphtheria consists of applying with a cotton swab a 2 per cent aqueous solution of potassium tellurite to the suspected throat lesion. In the presence of diphtheria the lesion turns black. While not infallible, the test appears to be very helpful in making a rapid bedside diagnosis.[11] Mueller's[12] studies on the metabolic requirements of the bacillus have led to luxuriant growths on special culture media.

The following experiment explains the essence of what can be expected from antitoxin. If a standard unit of diphtheria toxin is injected

into a guinea pig of a certain weight, the guinea pig will die; but if within fifteen minutes this guinea pig is given a unit of antitoxin, the toxin will be neutralized and the animal will suffer no ill effects. However, this dose will not suffice if given later. In fact, if we wait two hours and a quarter, a dose one thousand times as great will not save the animal. When we realize that 1000 units of antitoxin to a guinea pig corresponds to 100,000 units for a fifty-pound child, we can easily understand why enormous doses of antitoxin so often fail to save malignant cases. The time element, therefore, is of the utmost importance, and in rapidly fulminating cases every hour counts. Thus, when it comes to the dose of antitoxin to be administered, the question is comparable to how much water it takes to put out a fire. However, the following table may be used as a guide.

Recommended Dosage of Antitoxin

Weight of Patient	Type of Disease		
	Mild	Moderate	Malignant
	units	*units*	*units*
Under 50 lb.	5,000	10,000	50,000
Over 50 lb.	10,000	20,000	100,000

In severe cases the intravenous route is preferable, but this may be combined with the intramuscular route. A single dose may be sufficient, but in severe cases additional doses are often given.

The toxemia itself produces an apathy, listlessness and finally stupor, but if the membrane and edema obstruct respiration, restlessness becomes prominent. In several contagious hospitals it is now the rule to avoid all opiates during this stage because sedative drugs mask this restlessness, which at times may be caused by a small piece of loose membrane which can be easily removed by suction. In fact, suction can sometimes obviate the necessity of intubation. This toxemia is simply a very marked form of the toxemia found in other acute infectious diseases. Dehydration often occurs as the result of difficulty in swallowing. The carbohydrate metabolism is disturbed and a vascular collapse is threatened. Intravenous dextrose (glucose) 10 per cent is indicated in all but mild cases. The addition of insulin has not been shown to be effective.[13]

In the convalescent stage — that is, when the membrane is receding or after it has entirely disappeared — myocarditis may become evident. Every type of cardiac irregularity may occur, but a gallop rhythm and evidence of heart block are ominous signs, of which the latter is the more serious. The electrocardiogram may show a high degree of block before this is suggested by clinical observation. Advanced block may occur suddenly and proceed rapidly. The contractile fibers may also be involved, as shown by inversions of the T wave in all three leads, but often there is a combination of damage to the specialized conduction system and of injury to the myocardium in general. It is thought by many that drugs of the digitalis group are contraindicated since they might tend to promote block. One has but to appreciate the pathology of a diphtheritic myocarditis to understand the futility of the various drugs employed.

During convalescence vascular collapse of a different order from that seen in the toxemic stage may take place. This is brought about as part of the postdiphtheritic polyneuritis, and is due to a paralysis of the motor end plates of the splanchnic vessels. This results in a marked engorgement of the splanchnic vessels with marked pallor of the skin, epigastric pain and vomiting. This usually supervenes on myocarditis, and therefore throws a burden on an already damaged heart. Adrenalin is not powerful enough to overcome this condition, but Pitressin (beta-hypophamine) may be helpful. Warmth from an electric light bulb under a tent is sometimes helpful. A prolonged rest in bed of six weeks is indicated whenever a diagnosis of myocarditis has been established. Needless to say, the place for the care of all cases of diphtheria — except the mild forms — is a hospital equipped with the proper facilities.

The control of diphtheria can be achieved through immunization with the toxoid or with toxin antitoxin. The best results appear to have been obtained by three doses at four-week intervals.[14] One dose of the alum precipitate has given the poorest results, but this method has been recently modified by following it with three to six nasal installations seven days apart.[10] When diphtheria raged in New England the greatest number of cases and the highest mortality took place in children below the school age. Therefore, early immunization is desirable. Control, like the treatment, of diphtheria consists primarily of sound, protective measures applied early.

MENINGOCOCCAL MENINGITIS

The meningococcus has been shown to be a frequent inhabitant of the nasopharynx of healthy individuals. Thus, in groups enjoying good health, the carrier rate has been reported from 2 per cent to as high as 54 per cent, with no cases of cerebrospinal meningitis occurring in these groups.[15] It was formerly held that the carrier rate increases with an outbreak of the disease. The studies of Kuhns[16] at two CCC camps in Missouri do not substantiate this theory. In one

camp, in which 9 cases of the disease occurred, positive cultures of the meningococcus from the nasopharynx were found in 4.4 per cent of the men, while in another camp twenty miles distant, where there were no cases, positive cultures were obtained in 3.5 per cent. When one considers that positive cultures were obtained in as high as 54 per cent in a group of healthy individuals without the presence of a single case, it becomes clear that taking cultures of contacts is of very doubtful value as a control measure.

Another theory which has had to yield to the results of investigations is that the type of organism gives some clue to its virulence. We now know that all four types of the meningococcus may be virulent and cause serious outbreaks.[15] Furthermore, by typing all cases of the disease over a period of years it has been found that one type may be superseded by another in its predominance. In this the disease differs from pneumonia.

Antimeningococcus serum is polyvalent and thus contains agglutinating properties for all four types. Its efficacy depends on how early it is administered and how often it is administered as well as on the dose. Without serum the mortality was 80 per cent. In cases treated early with the serum the mortality is now between 6 and 20 per cent. Sulfanilamide appears to be effective in this disease, both alone and more especially in conjunction with serum treatment.[17, 18]

WHOOPING COUGH

In Massachusetts 80 per cent of all the deaths from whooping cough occur in the first year of life and 96 per cent occur in the first two years. The newborn appear to lack that relative immunity which they have for measles, mumps, scarlet fever and diphtheria. Therefore, every effort should be made to protect them from exposure. Bronchopneumonia is the commonest complication and often results from additional infections such as influenza, measles and common colds. Encephalitis may result from a superimposed latent neurotropic virus.[19] In rare cases convulsions are the result of tetany, but for the most part they are due to inefficient cerebral circulation during paroxysms.[20] These may be diminished by an oxygen tent and by barbiturates. The neurologic complications have been reviewed by Eley.[21] The heart is not permanently injured by the paroxysms.[22]

The early clinical diagnosis of whooping cough is generally made on the circumstantial evidence of exposure and an afebrile, paroxysmal and spasmodic cough which increases in severity and is generally worse at night. The white-cell count shows a gradually increasing leukocytosis with a high lymphocyte percentage. Cough droplet cultures yield *Hemophilus pertussis* in about 80 per cent of cases in the catarrhal stage, 60 per cent in the first week of the paroxysmal stage, 30 to 35 per cent during the second week, 15 to 20 per cent in the third week and 2 to 5 per cent in the fourth week. In keeping with this, it was found that in 70 per cent of whooping cough cases the patients were infected by exposure to individuals in the catarrhal stage.[23]

The present status of pertussis vaccine in the prevention of whooping cough has been reviewed by Maxcy.[24] He shows that up to 1931 the available evidence failed to establish the prophylactic efficacy of vaccines. Since then, however, progress in the cultivation of *H. pertussis* has resulted in the production of vaccines with definite immunizing power more in line with those of other antigenic agents of well-recognized value. The etiologic relation of *H. pertussis* to whooping cough has been firmly established,[25] and it has been shown that this organism in the course of cultivation undergoes changes during which its antigenic element, toxicity and infectiveness diminish markedly. Only in its primary, fresh, smooth phase is it effective for immunizing purposes. This explains the variable and unsatisfactory results obtained in the past. Sauer[26] has used these fresh preparations in total doses of 70,000,000 to 80,000,000, or four times greater than those previously employed, with results which leave no doubt as to its efficacy as a preventive. Maxcy's excellent and critical review of the results obtained by Sauer and others with this new preparation deserves scrutiny by those whose opinions of the merits of pertussis vaccine date back to its previous doubtful status.

Maximum protection is not to be expected until about four months after the completion of three or four bilateral subcutaneous injections of Sauer's vaccine at intervals of one week.[27] It should be kept in mind that such protection is not absolute but relative. Furthermore, on this basis little if any value can be expected from this measure as a preventive after exposure has taken place, to say nothing of when the disease is already under way.

The difficulties at present lie in the fact that there is no reliable method of standardization; consequently the dosage remains arbitrary. Furthermore, the antigenic substance contained in this newer preparation has not yet been identified. Consequently, commercial preparations are apt to vary in their potency. The most severe reactions are unfortunately apt to occur in very young infants, the very ones who need protection most. A severe reaction, however, is not so dan-

gerous at this age as is a severe attack of whooping cough.

MUMPS

In 1934 and 1935, Johnson and Goodpasture[28] established that mumps is caused by a filterable virus. This virus was obtained from the fresh saliva of mumps patients during the first two days of the parotid swelling, as determined by transfer to monkeys through injection of the parotid duct and back again to infect non-immune human volunteers through spraying the mouth.

Silwer[29] in 1936 and Finkelstein[30] in 1938 confirmed the findings of previous French observers of a latent encephalitis in the course of mumps. This consists of the finding of varying numbers of lymphocytes in the spinal fluid without any clinical signs or symptoms to suggest the presence of meningoencephalitic involvement. The cells counts in these cases ranged from 11 to 880 cells per cubic millimeter. I have recently seen a case of this kind with a cell count of 400. The frequency with which this occurs is unknown because routine punctures are not done in this disease. The fact that it does occur is evidence of the mildest form of neurotropic activity of a virus.

Clinical evidence of mumps encephalitis appears to be present in almost 10 per cent of adult cases, but the great majority of these are mild in character. It is indistinguishable from the condition found in preparalytic poliomyelitis except by the circumstantial evidence of the existence of mumps. Only rarely does it produce severe symptoms. The treatment is lumbar drainage.

Severe orchitis may be helped by early incision of the tunica albuginea, bringing about a rapid fall of a high fever, and apparently avoiding subsequent atrophy, as determined by follow-ups.[31] Owing to the long incubation period, mumps convalescent serum is very effective as a preventive if administered within the first week after exposure, but such passive immunization is of short duration.* Statistics fail to give convincing evidence that complications are reduced when the serum is administered after the disease is in progress.

MEASLES

An important step in the prevention of measles has been the development of human placental immune globulin by McKhann.[32–35] Progress is being made in the effort to improve this product whereby its ill effects will be minimized and its potency stabilized. Karelitz[36] recommends the globulin fraction of immune adult serum. When these are brought to a satisfactory stage in commercial development they bid fair to replace the use of convalescent serum and adult immune serum. All these materials are now being used to prevent or modify the disease. The protection afforded by them is of short duration, but it is of distinct value for two or three weeks. In order to prevent the disease they must be given within a few days of exposure. In order to modify it they must be given approximately one week after exposure, and modification cannot be expected in all cases so treated. The advantage of modification lies in the apparent permanent immunity.[37] After all, measles is a good hurdle to get over, and if the patient is over four years of age and healthy it is not to be dreaded. Circumstances, however, often make prevention or modification desirable.

POLIOMYELITIS

The researches of Aycock into the epidemiological characteristics of poliomyelitis indicate that it is due to a rather widespread virus infection of the upper respiratory tract, which may involve the gastrointestinal tract. Like the meningococcus, it gives rise to characteristic symptoms only when it gains access to the nervous system. This theory implies that there must be carriers among the population, but also that the great majority of the population become sooner or later immune through unrecognizable attacks.

There is no reliable specific serotherapy for poliomyelitis. Convalescent serum has never been established as of value once the disease is in progress, either in the preparalytic or paralytic stage.[38] If an immune serum could be so concentrated that much greater doses were possible than those now available some benefit might be expected. This does not mean that we should refuse serum if it is demanded, because, after all, the medical profession is entirely responsible for the present demand. Violent opposition to an impetus of this magnitude is dangerous.

Two methods of control have been attempted in the past five years. One of them has been to give subcutaneous injections of the virus.[39] If dead virus was injected no specific resistant response followed. On the other hand, if the virus was alive, even though attenuated, such injections sometimes were followed by the disease itself.[40] While the spraying of zinc sulfate, picric acid and alum appears to afford some protection to monkeys from the experimental disease, there is no good evidence that this method has been protective against the natural disease in human beings. The possibility of injury to the nasal mucous membrane by these chemicals might well

*Convalescent serums of all kinds can be purchased and obtained by air mail from the Manhattan Serum Center in New York City (Dr. William Thalhimer, director).

break down those important barriers to infection, and subsequently open the way to sinus infection and possibly to central-nervous-system involvement of this or other infectious agents inhabiting this area. Until a non-injurious, specific, chemical agent is found, it would appear wise to explain our limitations to those who turn to us for guidance.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT, M.D.

TRACY B. MALLORY, M.D., *Editor*

CASE 25431

PRESENTATION OF CASE

A thirty-nine-year-old Russian-born Jewess was admitted to the hospital complaining of pains and swelling in the extremities and of cough.

The patient stated that she had always been well and active until eight months before admission when, while working as a clerk in a department store, she was suddenly seized with a constant, non-radiating sharp pain in the calf of the right leg while standing. She continued to work for the remainder of the day. She returned home and went to bed, where she remained for five to seven weeks under the care of a physician. The latter stated that the leg was swollen from ankle to knee and that it was tender, especially along the course of the superficial veins, which felt "hard, like cords." She improved slowly and six months before entry returned to work. Ten days later, however, a severe sharp pain was noted in the right chest, which was made worse by breathing. She again went to bed and three or four days afterward developed a hacking cough productive of about a fourth of a cupful of thick, yellowish, non-foul smelling, occasionally blood-flecked sputum. This cough and chest pain persisted for about three months, but three weeks later the tissues and lymph nodes in the right half of the anterior neck became swollen and markedly tender. The neck veins became enlarged, dark blue, firm and "cord-like," but disappeared in three weeks. The right arm and left leg became similarly involved, so that they were swollen, tender and faintly cyanotic, and the palpable veins "cord-like." These symptoms slowly subsided until six weeks before admission, when the patient, still abed, noted an increase in the severity of her cough so that she had paroxysms with the raising of foul-smelling, heavy, yellow, rarely blood-flecked sputum, which nauseated her and occasionally caused her to vomit. Furthermore, she stated that the right chest pain which she had previously experienced was stabbing, aggravated by cough, and located in the right infraclavicular region. She said that x-ray films taken in an outside hospital six weeks before entry showed findings interpreted as being an "infarct." Two weeks before admission the patient thought that the ends of her fingers had become larger. During the present illness she was reported to have gained 16 pounds in weight. At no time had she experienced night sweats or fever. The patient further stated that she had had mild previously asymptomatic varicose veins for several years.

Her family history was noncontributory.

Physical examination revealed a slightly obese, tanned woman who was coughing up blood-stained sputum at frequent intervals. There were a few, almost healed psoriatic lesions over the right ankle and forearm. The right pupil was larger than the left. The throat was slightly injected. In both supraclavicular regions and in the left posterior triangle, were numerous tender nodules 0.3 to 2.0 cm. in diameter. The suprasternal dullness was slightly widened. Examination of the heart was negative. Examination of the lungs showed questionable amphoric breathing over the region of the right middle lobe. There was a moderate degree of clubbing of the fingers. The veins of the volar surface of the left forearm were tender and apparently thrombosed. There were very mild varicosities of the legs. There was no residual brawny swelling anywhere. A rectal examination showed only small internal thrombosed hemorrhoids. Nothing abnormal was felt in the pelvis. The introitus was virginal.

The temperature was 99°F., the pulse 88, and the respirations 24.

Examination of the urine on many occasions was essentially negative. The blood showed a red-cell count averaging 4,700,000 with 70 per cent hemoglobin, and a white-cell count which averaged 25,000 with 85 per cent polymorphonuclears. The stools were guaiac negative. Sputum culture showed a heavy, practically pure growth of monilia. A blood culture and Weil-Felix and undulant fever agglutination tests were negative. A blood Hinton test was negative. The electrocardiogram showed a ventricular rate of 75, with normal rhythm, upright T_1 and T_2 with flat T_3 and a tendency to low voltage. X-ray films of the chest revealed scattered areas of consolidation throughout both lung fields, which were confluent in both middle lung fields, particularly in the right middle lobe and in the anterior portion of the right lower lobe. In the left lung field there were multiple, round, poorly defined areas of increased density. Films of the hands showed slight soft-tissue swelling about the terminal phalanges, but the bones showed no evidence of osteoarthropathy. A gastrointestinal series was negative.

On the day after admission the temperature rose to 100.5°F., and remained at about this level throughout her stay. On the eleventh hospital day, after leading an uneventful hospital course, she

developed thromboses of two superficial vessels in the calf of the right leg, which were biopsied. Anaerobic and aerobic cultures were negative; the small vessels removed showed acute thrombophlebitis. Subsequently, at varying intervals, smaller lesions appeared on the wrists, arms and thighs. The patient slowly but steadily became weaker, and despite digitalization her edema persisted. Additional x-ray films of the chest showed no significant changes from those previously observed. One month after entry the patient suffered from two bouts of epistaxis. Examination revealed a bleeding point in the left nares, which was controlled by cauterization and packing. On the fiftieth hospital day she suddenly developed massive edema of the left arm and became markedly dyspneic. Edema of the legs increased in amount, and she died on the fifty-third hospital day.

Differential Diagnosis

Dr. Walter Bauer: "The small vessels removed showed acute thrombophlebitis." Was that a real thrombophlebitis?

Dr. Tracy B. Mallory: It might be fairer to say "acute thrombosis"—a fresh thrombus with no inflammatory reaction whatever.

Dr. Bauer: A real thrombosis?

Dr. Mallory: Yes.

Dr. Bauer: I do not believe there can be much doubt but that this woman fell ill eight months prior to admission. The question is, Was the initial illness related to what was subsequently found in her chest? I think there can be little doubt that she was suffering from migratory phlebitis or phlebitis migrans. The story is quite characteristic of this disease syndrome. Whether migratory phlebitis is a distinct disease entity, no one really knows. It is a relatively rare condition. I suppose it is more frequently encountered in thromboangiitis obliterans than in any other disease. It may be the first symptom of thromboangiitis obliterans. Involvement of the superficial veins is quite characteristic. It begins peripherally, disappearing in one area only to reappear at another a little closer to the heart. This patient was a woman. We know that thromboangiitis obliterans is a relatively rare disease in women. We have no other symptom suggesting its existence in this patient. With the premise of migratory phlebitis followed by a sudden attack of pain in the right chest one might reasonably conclude that this patient had what was diagnosed on the outside by a roentgenologist—a pulmonary infarct. However, I believe pulmonary infarction is rarely encountered in phlebitis migrans. This is due to the fact that the process starts externally and as a rule involves the external and middle coats of the vein. Complete resolution usually occurs in one portion of the vein only to have the process begin elsewhere. Pulmonary infarction is so infrequent that those working in the Peripheral Vascular Clinic do not advocate ligature of the vein in order to prevent pulmonary infarction. I think there are exceptions to this rule. Dr. Mallory can set me straight on this.

Dr. Mallory: My experience is limited, but the cases other than Buerger's disease on which I have seen a biopsy have shown thrombosis regularly, inflammatory reaction in the vessel walls rarely.

Dr. Bauer: The literature on this disease is very meager. The only place I looked it up was in Homans's textbook. Therein it states that in migratory phlebitis one rarely needs to worry regarding the possibility of pulmonary infarction because it occurs so rarely. This is due to the fact that the pathologic process proceeds from without inward.

Dr. Mallory: I think Dr. Homans believes that thrombosis can occur and spontaneously resolve very rapidly.

Dr. Bauer: That is obvious from the course of the disease. It may involve a vein in the region of the wrist or ankle with obvious signs and symptoms persisting for several weeks only to disappear completely. Later the same process may occur in the region of the elbow and subsequently higher up the arm. I think we have to be very cautious in interpreting these chest x-ray films. Ordinarily we should say that sudden pain in the chest occurring in a patient with phlebitis means pulmonary infarction. Infarction with infected emboli should cause tissue necrosis, cough and foul-smelling sputum. We are unable to state just what the situation was in this case. It is of interest that there was a two months' interval between the onset of the first venous thrombosis and the appearance of sudden severe pain in the chest. At this time there was no evidence of phlebitis. To have a pulmonary embolus at this late date would be unusual. The fact that this patient had no fever is another reason for wondering if the pleural pain was not due to some cause other than pulmonary infarction. This pain persisted from the very onset. You might argue that she had had an infected pulmonary infarct with subsequent abscess formation, lasting three and a half months. This would be unusual in the absence of fever. The fact that her temperature was only 99°F. on entrance is significant. The sputum which she raised was always blood streaked. This is rather unusual, is it not, Dr. King, in the

case of pulmonary abscess or an infected pulmonary infarct.

DR. DONALD S. KING: Yes.

DR. BAUER: This bit of evidence is helpful. She did have a leukocytosis running around 25,000. She developed enlarged supraclavicular lymph nodes. One might argue that they were part and parcel of the phlebitis. However, they persisted despite the fact that the phlebitis disappeared. I wish the description of these lymph nodes was more detailed. They were tender. Were they firm or hard? I should be inclined to believe that this woman was suffering from a migratory phlebitis but that in addition she had cancer of the lung. We shall have Dr. Hampton discuss the x-ray films in greater detail a little later. I should be inclined to believe she probably had metastatic carcinoma of the lung rather than a primary tumor. If she was suffering from metastatic carcinoma, where was the primary tumor? I believe that the supraclavicular nodes were "sentinel nodes." I may be wrong, because it is possible for inflamed lymph nodes to persist that long. The continued blood streaking and absence of fever would fit pulmonary cancer better than pulmonary disease in consequence of repeated pulmonary infarction, regardless of whether or not the emboli were infected. These metastatic lesions were bilateral. They may have been secondary to carcinoma of the breast or hypernephroma. Dr. Hampton, can the metastases of hypernephroma be relatively diffuse?

DR. AUBREY O. HAMPTON: They could be similar to those in this case.

DR. BAUER: We know she had some red blood cells in the urine. If I were to guess, I should say that her primary lesion was a hypernephroma and that she had metastases to the lungs. I think it is highly probable that this woman's exitus was due to a pulmonary infarct. I do not believe that repeated pulmonary infarction alone explains the entire situation. I shall say what I think before Dr. Hampton discusses the x-ray films. If I have reason to change my mind later I hope that I shall be allowed to do so.

I shall summarize by saying that this patient had a hypernephroma with bilateral metastases to the lungs, and migratory phlebitis. She probably died because of a pulmonary embolus. I doubt if she had the generalized form of pulmonary osteoarthropathy, for no generalized bone pain was present; she did, however, have the localized form.

DR. F. DENNETTE ADAMS: Do you attach any significance to the report of monilia in the sputum?

DR. BAUER: I am happier leaving that finding alone rather than trying to attach any significance to it.

DR. KING: On the wards the therapeutic attack was on the basis of the infection with monilia and large amounts of iodide were given.

DR. BAUER: That is all right by me, but I should prefer to leave the monilia alone because I think it is a red herring. I may be wrong, because I do not know anything about yeast infections of the lung.

DR. HAMPTON: I am sure this chest picture changed in the time between the outside examination and this one. These quite sharply defined round areas in the left lung could not be infarcts. They are due either to metastatic abscesses or to metastatic carcinoma. The shadow that was interpreted as infarct does look somewhat like one, if you believe infarcts are triangular in shape.

DR. MALLORY: How about a septic infarct?

DR. HAMPTON: Septic infarcts or metastatic abscesses could produce this picture. This triangular shape appears at the base of the upper lobe—the middle lobe is not involved particularly, no more than any other part of the lung; however, the lesion looks more like one due to collapse of a portion of the upper lobe than to an infarct. I cannot say positively that it is not an infarct, but it is more like collapse. Certainly if it is an infarct it has been there long enough to reduce the lung in size and to become very sharp in all directions and more like a triangle than an infarct should be. Over a period of months we have evidence of increase in size of this area of density, thus indicating a progressive disease without pleural fluid, and in this spot film you see a very definite round mass. I do not know which side this mass occupies, but I assume it is in this area here at the right. She did have swelling of the soft tissues around the terminal phalanges without bone changes.

DR. BAUER: Could such an x-ray picture be secondary to a primary cancer of the lung?

DR. HAMPTON: Yes.

DR. BAUER: Would you be inclined to think that this lesion here, plus the other findings, was consistent with metastatic carcinoma?

DR. HAMPTON: I could not explain the triangle on the basis of cancer, but I could account for the round mass on the basis of metastasis.

DR. BAUER: Is it fair to ask Dr. Hampton to make a diagnosis?

DR. MALLORY: Yes, at this stage.

DR. BAUER: I do not believe I shall change mine.

DR. HAMPTON: I should explain the small focus at the base of the right upper lobe as being due to a primary tumor. It could, however, be due to metastatic infection or to metastatic malignancy.

DR. BAUER: Let us leave for a moment the question as to whether it is primary in the lung or elsewhere. If we make a diagnosis of malignancy are you willing to make in addition a diagnosis of pulmonary infarction?

DR. HAMPTON: No.

DR. BAUER: What would be the easiest way to explain the exitus?

DR. HAMPTON: That triangular lesion could be an infarct. We did not have a film taken after death, which would show the infarct if it happened at that time.

DR. BAUER: I shall leave it that way. I was not able to interpret whether this was primary carcinoma of the lung or the result of metastases.

DR. MALLORY: There is one other piece of information which was withheld. I do not believe it would have helped you much. One of the lymph nodes in the neck was biopsied and showed an unclassified malignant tumor, probably a carcinoma.

DR. KING: What do you think about the recurrent hemoptysis in relation to whether it was primary or metastatic cancer of the lungs?

DR. BAUER: It would fit primary carcinoma of the lung much better. If I had given that more thought, even though I did not have the expert interpretation of the x-ray films, I should have come nearer to making what I now believe is the right diagnosis, namely primary carcinoma of the lung.

DR. J. H. MEANS: I should like to speak on one point. I did not have this patient in charge but saw her once on teaching rounds. I agree entirely with Dr. Bauer's thought that she had a migratory phlebitis. He raised the question whether you can get embolism in this disease. I shall merely cite a patient of mine who I think had the same disease. He did have a series of pulmonary emboli with infarcts but without any infection, as in this case. These cleared up rapidly. After he had had his tonsils out and had his epidermophytosis cleared up he recovered. Whether that had any relation to the migratory phlebitis, I do not know; but Dr. Arthur W. Allen who saw him in consultation expressed the belief that a fungous infection might play a role in the etiology of migratory phlebitis. I mention the case because of the embolism. I am sure it may occur.

DR. BAUER: Yes, but as I have said it is so rare that ligation is not indicated.

There is one other point about thromboangiitis obliterans. At the Mayo Clinic they have tried to prove that it is an infectious disease. The evidence thus far is not very convincing.

CLINICAL DIAGNOSES

Carcinomatosis.
Phlebitis migrans.

DR. BAUER'S DIAGNOSES

Carcinoma of the lung (? primary, ?metastatic), with widespread pulmonary metastases.
Phlebitis migrans.
Pulmonary infarct.
Pulmonary osteoarthropathy.

ANATOMICAL DIAGNOSES

Primary carcinoma of the lung, right middle lobe, with extension and metastases to opposite lung, mediastinum, pericardium, pleura and lymph nodes.
Thrombophlebitis of femoral and common iliac veins and inferior vena cava.
Hydrothorax.
Hydropericardium.
Leiomyomas of the uterus.
Atherosclerosis of the aorta and coronaries, minimal.

PATHOLOGICAL DISCUSSION

DR. MALLORY: So far as the migratory phlebitis of Buerger's disease is concerned, in the acute stage it regularly shows a highly specific picture with multiple miliary lesions made up of monocytes and giant cells that suggest miliary tubercles or gummas. This patient did not show any such picture. I think that is an important point against Buerger's disease as the cause of the phlebitis in this case.

The autopsy showed that the primary lesion was in the middle lobe of the right lung. It was a nodule of cancer about 5 cm. in diameter, surrounding and growing into the primary bronchus of the right middle lobe. There were multiple metastases throughout both lungs, the result of extension both through lymphatics and the blood stream. Metastasis had occurred to other parts of the body. Many of the retroperitoneal nodes were involved, as well as those that you have heard about in the neck. The phlebitis was very extensive and involved a great many large veins as well as small ones. In fact both femorals, both iliacs and the inferior vena cava itself for a distance of 8 cm. were filled with thrombus. Why an embolus had not broken off I cannot imagine, but there was not a single infarct in the lungs.

DR. BAUER: You have not explained the sudden exitus.

DR. MALLORY: No. A possible thing was that she had a carcinomatous pericarditis with a significant amount of fluid — 300 cc.

DR. BAUER: Cardiac tamponade?

DR. MALLORY: Perhaps. Three hundred cubic centimeters of fluid would not produce tamponade in a normal pericardial sac but with the walls stiffened and rendered inelastic by cancer it might.

DR. BAUER: I should think the mistake I made was in not interpreting the continuous blood streaking correctly. I should have realized that that would be rather unusual with metastatic carcinoma.

DR. KING: We have seen a few cases, about three or four, where hemoptysis has occurred with metastatic malignancy.

DR. HAMPTON: That discussion came up some time ago. We looked it up after a fashion, and as we reviewed the cases that were treated in the Tumor Clinic we found that metastatic carcinoma very rarely produces hemoptysis.

DR. BAUER: That is very significant. If I had interpreted it properly I should have made the correct diagnosis the first time. Such points are extremely important to remember.

CASE 25432

PRESENTATION OF CASE

A thirty-eight-year-old woman was admitted to the hospital, from a tuberculosis sanatorium, complaining of malaise.

The patient had been in a weakened and run-down condition for ten or fifteen years, with poor resistance to respiratory infections, and an inability to gain weight. She had suffered repeated attacks of severe "colds" and had seven severe attacks of quinsy during the past eighteen years. The most recent and severe peritonsillar abscess occurred two and a half years before admission and required two separate incisions, with drainage of large amounts of foul-tasting pus. On all occasions the abscesses were incised without anesthesia, and she recalled having aspirated none of the draining purulent material. The patient stated that the tonsils were partially removed in infancy but that she had not been able subsequently to have a complete removal. Much of the patient's life had been spent in England, Australia and Canada. She was fairly well until sixteen months before admission when she contracted a severe "chest cold and bronchitis" similar to many other attacks she had experienced in the past. She had the usual course of a cold for a few days, after which there remained a persistent hard cough which was productive of not more than a teaspoonful of yellow, non-foul sputum. There were no other symptoms save weakness and easy fatigability. X-ray films were taken which confirmed the clinical diagnosis of pulmonary tuberculosis. The x-ray findings were reported as showing infiltration of the right lower lobe, and a small mass seen in the right hilus region was interpreted as being an enlarged lymph node. The sputum was positive for tuberculosis. About fourteen months before admission she entered a sanatorium where bed rest and supportive measures were instituted. She improved rapidly both subjectively and objectively so that she gained weight, felt renewed vigor and noted a subsidence of cough, although she raised about a teaspoonful of sputum a day for several months. For the first three months of sanatorium care the sputum was positive for tubercle bacilli; but since then the monthly sputum examinations had been negative. X-ray films were reported to show good improvement of the parenchymatous infiltration, but the mass in the region of the right hilus was observed to increase in size, with cavity formation. During the recent months before entry she had almost no cough except for a few days following each of three bronchoscopic examinations. Approximately one month before admission she awakened from an afternoon nap and found her mouth full of a large quantity of foul-tasting purulent material intermixed with blood. The taste resembled that of the material obtained from incision of her peritonsillar abscesses in the past. She was referred to this hospital for further study.

The physical examination showed a well-developed, well-nourished, healthy-looking woman in no distress. There was slight dullness posteriorly with diminished breath sounds and increased tactile fremitus and spoken and whispered voice from the fifth rib downward on the right. The remainder of the examination was negative. The temperature, pulse and respirations were normal. Blood and urine examinations were negative. The corrected blood sedimentation rate was 0.15 mm. per minute. Chest fluid injected into guinea pigs before hospital admission was found to be negative for tubercle bacilli. The blood Hinton test was negative. X-ray films of the chest revealed an oval mass at the apex of the right lower lobe in contact with the sixth and seventh dorsal vertebrae and extending from the sixth rib to the eighth interspace. The mass was 6.5 cm. in length and 4.5 cm. in width. An irregular cavity with a fluid level was present within the mass. The walls of this cavity were a little over 1 cm. in thickness. The periphery of the mass was smooth. There was definite thickening of the pleura overlying the vertebrae, presenting somewhat the appearance of an abscess around these vertebrae, but the vertebral bodies were normal and the joint spaces were preserved. The heart and mediastinum were slightly dis-

placed to the right, but there was no mediastinal shift with respiration. The left lung was clear. The right lung was also clear except for the area described and two small irregular areas, one at the apex and one at the base of the upper lobe. The diaphragm moved well.

On the eighth hospital day an operation was performed.

Differential Diagnosis

Dr. Alfred O. Ludwig: In this case we are faced with the necessity of explaining the nature of what appears to be an abscess. I do not believe we can get around the diagnosis of tuberculosis because it is very clear she had a positive sputum examination on many occasions. I wonder if Dr. Hampton will show the x-ray films first. There is no mention of plates of the cervical spine; I wonder if any were taken.

Dr. Aubrey O. Hampton: This patient brought some films with her. The most striking thing is, of course, this sharply defined oval mass in the apex of the right lower lobe which was described in the report. The mass had gradually increased in size over a period of several months, eventually breaking down in the middle, and now shows a very irregular thick-walled cavity. There was also a small round mass at the base of the right upper lobe, which, during the period the large one increased in size, diminished and almost disappeared. The spine does not show anything abnormal. There was an attempt at connecting this lesion in the lung with the pleura, but this was not successful.

Dr. Ludwig: There was nothing in the examination of the dorsal spine that allowed you to think there might be tuberculosis of the vertebrae?

Dr. Hampton: No; I was interested in demonstrating whether or not the pleura was adherent. If it were adherent you might get more evidence that it was an inflammatory lesion, but of course such a finding would not be sufficient to make a diagnosis.

Dr. Ludwig: I think, first of all, that this woman had pulmonary tuberculosis, but I do not believe it is possible to correlate the presence of pulmonary tuberculosis with this mass. The latter must represent some different process. The first thing I thought of as a possibility, which I dismiss, was that this woman might have had tuberculosis of the dorsal or cervical spine, with formation of a paravertebral abscess. I have never heard of such an abscess's occurring in this position. We have seen them appear in the region of the psoas muscle subsequent to cervical and dorsal vertebral lesions, so they can do strange things; but in the absence of positive x-ray findings anywhere in the spine I do not believe we have the evidence to make such a diagnosis. This woman did have peritonsillar abscesses but I do not believe we can relate these to the presence of tuberculosis. I cannot imagine that a peritonsillar abscess would heal as well as this one did, if it were of tuberculous origin. I should think it possible that this woman may have had a lung abscess secondary to peritonsillar abscess, but there are several things about such a diagnosis that are difficult to correlate with what we are given. In the first place the whole course is a strange one for a pulmonary abscess of the ordinary sort. She did have foul sputum, but so far as I can tell she never had much in the way of a febrile reaction. We are not told anything about leukocytosis; I think we have to assume it was absent.

Dr. Tracy B. Mallory: There was none on two counts that were done at this hospital. I do not know about the sanatorium findings.

Dr. Ludwig: Furthermore, the blood sedimentation rate was 0.15 mm. per minute, a normal figure, and this is another point against an active, septic process.

I am confused about the description given of the chest findings and shall ask Dr. King to help. "Slight dullness posteriorly with diminished breath sounds and increased tactile fremitus and spoken and whispered voice." To my mind the chest findings do not fit together. I should think if the patient had had partial collapse of the lung on the right there would have been diminished instead of increased tactile fremitus. If the bronchi were open I should think the breath sounds would have been increased rather than diminished.

Dr. Donald S. King: You cannot put much emphasis on these signs.

Dr. Ludwig: I imagine that the patient may have had partial collapse. Was there any x-ray evidence of that, or of partial bronchial obstruction?

Dr. Hampton: No. All we see is a mass occupying the apex of the right lower lobe. If it were primary in the bronchus, the latter would be so small that it would not produce any picture of collapse.

Dr. Ludwig: There was slight displacement of the heart and mediastinum to the right, but there was no mediastinal shift with respiration.

Dr. Hampton: The mass is not in the region of the right main bronchus, and the slight displacement of the heart might be blamed partly on scoliosis, which she had, and partly on scarring of the right upper lobe from old tuberculosis.

Dr. Ludwig: We have no evidence of pleural effusion, except that chest fluid was injected into

a guinea pig. She might have had an effusion previously.

DR. KING: The physical signs could be signs of a mass with some compression of the lung.

DR. LUDWIG: The diagnosis of pulmonary abscess of the ordinary sort is a very unsatisfactory one, I believe. She did bring up some blood at one time.

DR. MALLORY: One point worth considering is that there was no objective evidence as to foul sputum. We have only her word for it.

DR. KING: She brought that out clearly herself. She was certain it was foul sputum and noted the same sort of taste she had experienced when the peritonsillar abscesses broke.

DR. LUDWIG: This woman probably had a pulmonary abscess which suddenly drained at that time. It would be interesting to know what the febrile course was before and after the time she awoke and found the foul sputum in her mouth. She was probably afebrile because the abscess was relatively well drained for the time being. I wonder if the cavity could have been due to tuberculosis with secondary infection. It is nothing like the ordinary tuberculous cavity, and with the disappearance of the other lesion I do not believe we can hold to that point of view.

How about tumor? So far as I am concerned it could be possible. I should like to ask Dr. Hampton about that.

DR. HAMPTON: That was the great argument. Because of the thick wall, the sharp peripheral outline and the broken-down irregular center the lesion grossly suggests tumor more than anything else, but there was a round nodule in the base of the right upper lobe which disappeared.

DR. LUDWIG: Is there any possibility that this lesion was of the type that we have seen in sarcoid at the hilus?

DR. HAMPTON: No.

DR. LUDWIG: Is it not true that they never break down?

DR. HAMPTON: Yes.

DR. LUDWIG: If there were lymphoma, there is no evidence elsewhere in the body, and again I do not believe lymphoma breaks down.

DR. HAMPTON: Rarely.

DR. LUDWIG: I shall make the diagnoses of pulmonary tuberculosis and pulmonary abscess which was probably metastatic from a peritonsillar abscess and which had increased in size and then drained. The reason we have so little evidence of inflammation and activity is that the abscess had drained. Pulmonary abscesses may be caused either by aspiration or by septic pulmonary emboli from the region of infected tonsils or elsewhere. Dr. King, can you tell us what the present feeling is about that?

DR. KING: It depends on whose opinion it is. In this hospital we believe that the aspiration theory explains the great majority of cases.

DR. HAMPTON: If the patient had a chronic lung abscess, would not the wall of the abscess be thin?

DR. LUDWIG: I should think it would be thick.

DR. KING: The more chronic the abscess the thinner the wall. Is that right, Dr. Mallory?

DR. MALLORY: I am not sure. By x-ray that might seem to be the case as the surrounding area of consolidation cleared up. I do not believe we have ever seen an abscess wall as thick as this one was.

DR. LUDWIG: That knocks the props out from under my diagnosis. If it is a tumor, it is a strangely behaving one. I shall stick to my original diagnosis.

DR. MALLORY: The films on this case have been around the country and a great variety of diagnoses have been made. The field is open if anyone would like to make further suggestions.

A PHYSICIAN: How about hydatid cyst? She had been in Australia.

DR. HAMPTON: A hydatid cyst has a very thin wall.

DR. ALLEN G. BRAILEY: Is not two and a half years from the last peritonsillar abscess something of an objection to a diagnosis of lung abscess?

DR. MALLORY: Yes; that is a good point.

DR. KING: This case was presented to a board of experts at an "Information Please" contest which Dr. Holmes arranged for the National Tuberculosis Association. The diagnosis made there by the experts was the same as that which has been made by Dr. Ludwig, but if this performance had been conducted as the regular radio program it would have cost the sponsoring company ten dollars.

PREOPERATIVE DIAGNOSIS

Tuberculoma.

DR. LUDWIG'S DIAGNOSES

Pulmonary tuberculosis.
Pulmonary abscess.

ANATOMICAL DIAGNOSIS

Tuberculoma of lung.

PATHOLOGICAL DISCUSSION

DR. MALLORY: This lobe was resected by Dr. E. D. Churchill, who in the course of the operation noticed several little nodules on the pleura which he believed were very suggestive of tuberculosis. When the lobe was finally removed and sectioned a very large caseous mass was found at the apex of the lobe, with four or five smaller scattered

lesions elsewhere. The lesion was almost completely filled with caseous material. The cavity did not appear so large in the specimen as it did in the x-ray plates, and the diagnosis is tuberculoma. It is a type of reaction to the tubercle bacillus that is not uncommon in other organs, but we do not often see it in the lung. The vast majority of such lesions break down and form a cavity.

DR. KING: The nodular or circular lesions of pulmonary tuberculosis are recently receiving a good deal of attention because they are very easily confused with pulmonary tumors. There are reports in the surgical literature of cases operated on for carcinoma that have proved to be due to tuberculoma. Most of the circular lesions are smaller than the one in this case. Sometimes the round lesion is the end stage of a primary infection and remains healed, but in our experience at the Middlesex County Sanatorium these lesions are very apt to develop a cavity in the center, giving a doughnut type of shadow in the x-ray; these doughnut-like lesions usually spread rapidly.

DR. HAMPTON: I wish we had the other films. She had a small tuberculoma in the base of the right upper lobe that disappeared.

DR. LUDWIG: Is it not somewhat unusual to have a tuberculous cavity appear in this situation?

DR. HAMPTON: No.

DR. LUDWIG: As close to the spine as this one?

DR. HAMPTON: We used to think so, but since the chest surgeons have been collapsing cavities we have found quite a few.

DR. LUDWIG: Was there any other organism in this tuberculoma?

DR. MALLORY: We did not culture it. The slides, however, do not suggest any secondary infection.

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NEW ENGLAND POSTGRADUATE ASSEMBLY

The second New England Postgraduate Assembly will be held on Tuesday and Wednesday of next week at Sanders Theatre, Harvard University, Cambridge. Invitations have been sent to every registered physician in New England, and the applications for badges and tickets already received by the committee indicate that the attendance will be even greater than that in 1938, when approximately nine hundred physicians were registered. This year's meeting is officially sponsored by the Massachusetts, New Hampshire and Rhode Island and Vermont State Medical Societies and the Maine Medical Association.

Last year's program was received so enthusiastically that no change in the general scheme has been made by the Program Committee. Eleven carefully chosen guest speakers, all prominent educators as well as successful practitioners in their particular fields of medicine, will deliver twenty-two thirty-minute talks on subjects of practical and timely interest; there will be no discussions. Buffet luncheons will be served in Memorial Hall on both days, and will be followed by an address on Tuesday and a question period on Wednesday. The dinner on Tuesday evening, also served in Memorial Hall, will be followed by a talk by a member of the Federal Bureau of Investigation of the United States Department of Justice.

The registration fee (three dollars) does not include admission to the luncheons (fifty cents each) or the dinner (one dollar). Those desiring tickets for the latter should apply immediately, if they have not already done so, to the Postgraduate Assembly Committee, 8 Fenway, as only a limited number of tickets will be available at the registration desk in the corridor of Memorial Hall. Such applications should be accompanied by a check or money order, and if they are received by the committee on the week of the assembly, the applicant must claim his badge and tickets at the registration desk.

This is an unusual opportunity for all New England physicians to obtain the latest and best information in regard to the diagnosis and treatment of a variety of diseases, and it is hoped that but few will fail to make the most of it.

A NEW ORGANIZATION INTERESTED IN MEDICAL EDUCATION

In the later years of the nineteenth century, scientific contributions concerning the etiology of many diseases and the methods of dealing with them imposed on institutions engaged in educating physicians the responsibility of adjusting their methods to meet the demands of this revolution in medical practice. Some of the schools were progressive and adjusted their curricula to meet the situation. A considerable proportion, however, were poorly equipped, inadequately endowed or carried on for the financial benefit of the controlling interests, and among these, conditions were intolerable in many instances.

The first effort designed to bring about the indicated reformation was the enactment of state registration laws designed to protect the public from incompetent practitioners and also to bring about better educational methods in medical schools. It was hoped that medical schools would adjust their methods to provide better prepared candidates for state approval. Unfortunately most of the proposed laws were so modified before enactment that the situation throughout this nation was far from ideal because of the lack of uniformity of important provisions relating to medical pedagogy and the admission to practice of the graduates of schools the curricula of which were based on theories that were at variance with scientific knowledge. Some states had several registration boards operating under different standards of medical education, thereby enabling irregulars to practice medicine.

In 1904 the American Medical Association came to appreciate the necessity of more effective action within the profession and created the Council on Medical Education and Hospitals, with the avowed object "to investigate conditions of medical education, hospitals and associated subjects and to suggest means and methods by which the same may be improved." The officers of the Council took up the imposed responsibilities with enthusiasm, collected facts and recommended the retirement from the field of medical education of more than half of the then existing schools. This was brought about and today there are seventy-six medical schools in the United States and Canada recognized by the Council. Furthermore, medical schools, hospitals, the Federation of State Medical Boards of the United States, medical societies and educational institutions having direct or associated functions covering medical education are cooperating with the Council. Although it has no authority to compel adoption of its recommendations or standards, the quality of its work has inspired respect for its decisions and brought about among the faculties of the approved educational bodies a disposition to adopt, so far as possible according to local conditions, the standards defined in the Council reports.

Even with the creditable advances made in the last thirty-five years the opinion is current that modern medical education is not a static or perfectly organized plan for training physicians, as shown by differences in methods and standards in the curricula of various schools. As this sentiment pervaded the minds of those particularly interested in the matter, it was expressed in conferences of groups and brought to the attention of the Annual Congress on Medical Education and Licensure in Chicago in 1938, with the recommendation that representatives of those bodies interested in medical education should unite for the purpose of study and concerted action in bringing about progress in this field. This proposition was severely criticized in an editorial in the February 26, 1938, issue of the *Journal of the American Medical Association*.

The plan, however, was not abandoned, and on June 24, 1939, delegates from organizations interested in medical education, met and created the Advisory Council on Medical Education. The names of the delegates present at this meeting are as follows: William S. Middleton, M.D., Willard C. Rappleye, M.D., and Maurice H. Rees, M.D., of the Association of American Medical Colleges; Robin C. Buerki, M.D., Rt. Rev. Msgr. Maurice F. Griffin and Christopher G. Parnell, M.D., of the American Hospital Association; Rev. Fr. Alphonse M. Schwitalla, S.J., of the Catholic Hospital Association; Walter L. Bierring, M.D., Jesse W. Bowers, M.D., and the late Harold L. Rypins, M.D., of the Federation of State Medical Boards of the United States; Franklin G. Ebaugh, M.D., John Green, M.D. and Byrl R. Kirklin, M.D. of the Advisory Board for Medical Specialties; Arthur W. Allen, M.D., and Dallas B. Phemister, M.D., of the American College of Surgeons; Edwin B. Fred, Ph.D., and Clarence S. Yoakum, Ph.D., of the Association of American Universities; and Anton J. Carlson, Ph.D., of the Division of Medical Sciences, American Association for the Advancement of Science. The American College of Physicians, also a participating organization, had appointed J. Howard Means, M.D., and Hugh J. Morgan, M.D., as delegates, and the American

Public Health Association and the National Board of Medical Examiners had designated Walter S. Leathers, M.D., but neither was able to attend. Other organizations included, as voted at the meeting, are the Association of American Colleges and the American Protestant Hospital Association. The following officers were elected: Dr. Rappleye, president; Dr. Rees, vice-president; Dr. Buerki, secretary-treasurer.

The Council on Medical Education and Hospitals of the American Medical Association was invited to send delegates to this meeting, but since the Reference Committee on Resolutions of the House of Delegates of the Association had reported that this action was inadvisable, the invitation was not accepted; however, the committee submitted the recommendation that communications received from the new council should be given consideration. This action of the committee was construed by some as a wish to avoid an alliance which might not be advantageous to the official representatives of the American Medical Association, particularly in view of the fact that the Council on Medical Education and Hospitals of the American Medical Association had recommended the sending of delegates to the meeting.

Regardless of any interpretation of the purposes of the founders of this new organization, the constitution adopted by it should dispel suspicion of any antagonism to the American Medical Association or to the work of the latter's Council on Medical Education and Hospitals. The part relating to its proposed function reads as follows:

> This council is created to meet the need of a central agency representing the universities, medical schools, hospitals, licensing bodies, specialty boards, public-health agencies and other national organizations in this country which deal with different phases of medical education. The council shall serve as a clearing house for the co-operative consideration of those problems and programs of professional training with which more than one group is concerned; as a medium of consultation and mutual assistance in the formulation and support of adequate educational standards; and as an agency for advice and recommendations to member and other organizations dealing with medical education.

The study of this portion of the constitution and other information at hand warrants the belief that this council is not desirous of usurping the power and influence of any department of the American Medical Association. Its members regard the American Medical Association as the parent organization in this country and one which is entitled to the highest position in dealing with the problems relating to medical education. It is apparent that the council hopes to pattern its work on the general activities of the Medical Council of Great Britain. In general, the members realize that they have no executive power but hope to contribute advice as they see occasion for it and engage in the study of such problems as may be delegated to committees. At this meeting, committees were appointed to study conditions relating to interstate endorsement of medical licensure and the hospital-intern problem.

With these facts before us and with knowledge of the standing of the men behind this movement to create another group interested in medical education, it is reasonable to suggest that any suspicion of unworthy motives should be held in abeyance until there seems to be a foundation for it. By their works we shall know them.

OBITUARY

SETH MARSHALL FITCHET

1887 – 1939

Seth Fitchet was a robust individualist, a modest and sincere man, an able and sympathetic physician. He hated sham and pretense in others and he was never guilty of either himself. He enjoyed life, but he did not flinch when he knew that death for him was very near.

At the age of eighteen, justly believing that he had not received his proper reward at the hands of his teachers, he left school and enlisted as a seaman in the United States Navy, serving with the Pacific Fleet for four years. He was discharged with the rank of chief petty officer, and as the injustice which had been meted out to him in school had by then been corrected, he returned to finish his course. Failing any financial backing, his academic pursuits were necessarily carried out entirely on his own resources with the help of occasional scholarships.

He entered the Harvard Medical School with the class of 1919; but as soon as the United States entered the World War, he enlisted and after a preliminary period of training at Plattsburg was commissioned a captain in Battery E of the 301st Field Artillery.

During his training at Plattsburg he sustained a severe injury when a camouflaged gun pit caved in, fracturing several cervical vertebrae and leaving him after a prolonged convalescence with a slight residual paralysis. It was characteristic of the man that minor incidents such as this could not be allowed to interfere with duty, and with no complaints or incriminations, he carried on, went with his battery to the French front and was cited for bravery in action at Verdun and at Chateau Thierry. When the war was over he returned home as major and maintained his commission in the Reserve Corps until 1934, finally resigning as a lieutenant colonel.

When mustered out of active military service, he returned to the pursuit of his studies at the Harvard Medical School and graduated with the class of 1921.

After a surgical internship at the Massachusetts General Hospital, he entered private practice, maintaining, however, staff appointments both at the Children's Hospital and the Massachusetts General Hospital. In 1938 he became surgical director and chief-of-staff of the Josiah B. Thomas Hospital in Peabody.

Seventeen months before his death, he consulted one of his closest medical friends for what seemed to be a minor ailment. It was apparent, however, that the malignant disease from which he actually was suffering was already far advanced and no possibility of cure existed. In spite of this, Seth Fitchet, the soldier, returned to his work and remained at his post as long as he could — courageous and simple and victorious to the end.

A. T., Jr.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

Raymond S. Titus, M.D., *Secretary*
330 Dartmouth Street
Boston

Septic Abortion

Mrs. J. J., a twenty-four-year-old para II, was admitted to the hospital August 1, 1910, stating that she was approximately ten weeks' pregnant. Her present illness began three weeks before admission with chills and fever, which had persisted up to entrance. For the past seven days there had been severe lower abdominal pain and, for twenty-four hours, vomiting. The patient emphatically denied any attempt to induce an abortion. In the light of subsequent findings the truth of her denial is open to grave doubt.

The family history was not obtained. The patient's past history was uneventful. She had had no serious illnesses or operations. There had been one full-term normal delivery, with normal pregnancy and puerperium, two years before. Catamenia had begun at thirteen, were regular with a twenty-eight-day cycle and lasted five days. She stated that her last period had begun on May 15.

Physical examination showed a well-developed and nourished woman with a flushed face. The tongue was coated but moist. The temperature was 100°F., the pulse 102 and of good quality. The heart sounds were regular; no murmurs were heard. The lungs showed uniform resonance. The abdomen was soft, but tender in both lower quadrants, with slight muscular spasm. On vaginal examination there was a good multiparous perineum, a soft cervix and some blood-tinged vaginal discharge. The uterus was symmetrically enlarged to a size corresponding to a three or four months' pregnancy, differing from the patient's history. The vaults were tender, but no masses were felt. The white-blood-cell count was 12,000, the hemoglobin 90 per cent. The urine was clear, with a specific gravity of 1.008, and showed a slightest possible trace of albumin and no sugar. The sediment contained many leukocytes, red blood cells and epithelial cells.

The temperature rose steadily to 103°F. on the fourth day after admission, the pulse remaining between 100 and 110. The blood-tinged discharge continued. A diagnosis of septic threatened miscarriage was made, and it was deemed wise to empty the uterus. The cervix was dilated under ether anesthesia, and the cervical canal and lower uterine segment were tightly packed with sterile gauze. No apparent progress was made during the next twenty-four hours, so the pack was removed and another pack introduced without anesthesia. The patient quickly bled through the second pack. She was again etherized, and as she was bleeding freely, it was decided to complete the dilatation in order to empty the uterus. A fetus and placenta were extracted manually without injury to the cervix. No curet was used. The bleeding ceased when the uterus was emptied, and the patient was returned to bed in good condition.

The temperature, which had dropped to normal

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

just before delivery, rose again the following day to 102°F., and after a few days of elevation gradually fell to normal on about the fourteenth postpartum day.

The patient was discharged on the eighteenth postpartum day in good condition. The os was closed; there was a bilateral laceration of the cervix; the uterus was well involuted and in good position, and the vaults were clear.

Comment. This case well illustrates the conservative method of handling a threatened septic abortion. The continued rise in temperature and the small amount of bloody discharge were evidence that the contents of the uterus were infected. The size of the uterus — between three and four months — was definite evidence that the patient's story could not be relied on.

It is important in such cases that the uterus be emptied as gently as possible. Packing of the cervix and lower segment of the uterus for the purpose of softening the cervix and initiating labor is much safer than any attempt at instrumental dilatation and emptying the uterus at one sitting. It is quite possible in this case that had the second pack been left, in spite of the hemorrhage, labor would have started within the next twenty-four hours and the uterus emptied itself spontaneously. The hemorrhage which followed the second gauze packing was unquestionably initiated by the separation of some of the placenta. The rise in temperature to 102°F. on the day following the emptying of the uterus was definite evidence that infection existed. Strict conservatism was followed, no douches being administered; in the course of the next week the temperature gradually came down to normal, and the patient was discharged relieved on the eighteenth day.

Had an attempt been made to dilate manually this three-and-a-half-month uterus and empty it, tremendous hemorrhage would have resulted, requiring transfusion. Furthermore, the injury to the uterine wall which accompanies such a maneuver would undoubtedly have spread the infection. The uterus is very tenacious of its contents from three and a half to six months; if it has to be emptied, the more conservative the method chosen, the safer the operation.

MEDICAL POSTGRADUATE EXTENSION COURSES

This week marks the beginning of the Fall Session of the Medical Postgraduate Extension Courses, given by the Massachusetts Medical Society in co-operation with the Massachusetts Department of Public Health, the United States Public Health Service and the Federal Children's Bureau. Programs have been arranged in nine of the eighteen districts of the Massachusetts Medical Society, and printed schedules have been mailed to all physicians in these districts.

The courses include the following general subjects: cardiovascular disease, gonorrhea, syphilis, obstetrics, pediatrics, pneumonia, neurology, and head and spine injuries. However, the district programs have been made out according to the selections of the local committees. The eight or ten meetings in each district will be held at a specified time and place which have been so picked that they should be convenient for the majority.

* * *

The following sessions of the Medical Postgraduate Extension Courses have been arranged for the week beginning October 30:

BARNSTABLE

Sunday, November 5, at 4:00 p.m., at the Cape Cod Hospital, Hyannis. Cardiovascular Disease: Eleven important questions about heart disease and their answers. Instructor: Ashton Graybiel. Donald E. Higgins, *Chairman.*

BRISTOL NORTH

Thursday, November 2, at 4:00 p.m., at the Morton Hospital, Taunton. Cardiovascular Disease: Eleven important questions about heart disease and their answers. Instructor: R. Earle Glendy. Lester E. Butler, *Chairman.*

BRISTOL SOUTH (New Bedford Section)

Friday, November 3, at 4:00 p.m., at St. Luke's Hospital, New Bedford. Common Problems of Neurology: Indications for lumbar puncture. Instructor: T. J. C. von Storch. Robert H. Goodwin, *Chairman.*

ESSEX NORTH

Friday, November 3, at 4:30 p.m., at the Lawrence General Hospital, Lawrence. Syphilis in Pregnancy and the Offspring. Instructor: Rudolph Jacoby. John Parr, *Chairman.*

*ESSEX SOUTH

*MIDDLESEX EAST

MIDDLESEX NORTH

Friday, November 3, at 4:45 p.m., at St. John's Hospital, Lowell. Pneumonia. Instructor: Maxwell Finland. William S. Lawler, *Chairman.*

*WORCESTER DISTRICT (Milford Section)

WORCESTER DISTRICT (Worcester Section)

Friday, November 3, at 8:00 p.m., in the Staff Room of the Worcester City Hospital, Worcester.

*The course will be omitted October 31 because of the New England Postgraduate Assembly.

Gonorrhea in the Female. Instructor: Oscar F. Cox, Jr. George C. Tully, *Chairman.*

WORCESTER NORTH

Friday, November 3, at 4:30 p.m., in the Nurses' Home of the Burbank Hospital, Fitchburg. Complications in Obstetrics, Illustrated by Case Histories. Instructor: John Rock. George P. Keaveny, *Chairman.*

DEATH

SCANLAN — THOMAS J. SCANLAN, M.D., of West Roxbury, died October 18. He was in his sixty-eighth year.

Born in Oregon, he attended Tufts College Medical School, receiving his degree in 1903. During the World War, he served as a captain in the medical corps, having previously assisted the late Dr. Eliot Wadsworth in Red Cross work. At the time of his death Dr. Scanlan was chairman of the Board of Trustees of the Boston State Hospital. He had served as a member of the staff of the Boston Dispensary, consulting surgeon at Deer Island Hospital, medical examiner for the City of Boston law department, member of the gynecological staff of St. Elizabeth's Hospital, chief consultant at the Foxboro State Hospital and surgeon at the Winthrop Community Hospital.

Dr. Scanlan was a fellow of the Massachusetts Medical Society and American Medical Association and a member of the New England Obstetrical and Gynecological Society.

His widow, a sister and two brothers survive him.

EXPRESSIONS OF APPRECIATION

The following expressions have been passed by the Senior Staff of the Boston City Hospital in appreciation of Mr. Joseph P. Manning and Dr. George G. Sears, who have recently resigned from the Board of Trustees.

WILLIAM P. BOARDMAN, M.D., *President,*
Senior Staff, Boston City Hospital.

* * *

JOSEPH P. MANNING

For twenty-eight years a trustee of the Boston City Hospital; appointed trustee on April 28, 1911, resigned on May 1, 1939. For twenty-one years chairman of the Board of Trustees. On April 1, 1927, the trustees assumed management of the Boston Sanatorium, when this institution came under the jurisdiction of the Boston City Hospital as the Sanatorium Division.

The professional staff of the hospital wishes to acknowledge its appreciation of his contributions to the management and development of the institution during these years. Under his wise guidance it has grown from a collection of small two-story buildings to the present excellently serviceable, modern hospital. His honest and prudent disposition of large expenditures of millions of dollars has never been questioned by the taxpayers or by responsible city officials. His care and supervision in building and maintenance have shown a complete mastery of hospital administration. His patience and dignity, often in trying circumstances, eloquently preclude any criticism.

Lastly, may we attest to his high and understanding co-operation with the members of the professional staff; a dignified, courteous and fair hearing was always accorded them. The present renown and standing of the hospital is his monument.

It is our earnest wish that he may be with us for many years to enjoy the reward of a life fruitfully spent in the service of his fellow man.

GEORGE G. SEARS

Physician to the Boston City Hospital, active and consultant, for forty-six years; trustee for twenty-one years. A gentle and lovable physician, a distinguished teacher, a wise administrator. Recognized and honored by degrees from Amherst and Harvard for contributions to the medical world. A gentleman learned and scholarly, a large part of whose busy life was diligently devoted to the hospital he loved.

Appointed out-patient physician in 1893, he served faithfully through all the grades of the staff from the lowest to the highest. Returning as trustee in 1918 he gave to the hospital the benefit of his long years of close association with the institution. His thorough knowledge of the professional problems of the hospital brought a fine balance to the Board of Trustees and was of invaluable aid to the solution of its difficulties.

The professional staff of the hospital hereby records its sincere appreciation of his learning, his devotion and his long years of zealous service to the institution in whose growth from a small, undeveloped unit to its present enviable position he has had such a vital part. With grateful hearts, they salute him and wish him many years of health and happiness.

MISCELLANY

MAINE NEWS

RAGWEED SURVEY

Two pollen stations were operated for the 1939 ragweed survey, one at Portland on the roof of the Maine General Hospital and under the supervision of the hospital superintendent and the other at Camden under the auspices of the Camden Chamber of Commerce. These stations were opened August 10 and were continued for fifty days.

BOARD OF REGISTRATION OF MEDICINE

Physicians licensed to practice medicine and surgery in Maine on July 12, 1939, are as follows:

THROUGH EXAMINATION

William Champlin Burrage, Portland
Harry Edward Christensen, Portland
Joseph Francis Dinan, Boston
John Francis Dougherty, Bath
Edward Thomas Driscoll, Worcester, Massachusetts
Lucio Ernest Gatto, Cambridge, Massachusetts
Harold Floyd Gilbert, Mt. Holly, New Jersey
Napoleon Gingras, Augusta
Marlin Charles Moore, Kulpmont, Pennsylvania
Arthur Ames Nichols, Boston
John Coleman Nunemaker, Boston
Richard Rapp Owens, MacMahan Island
Maurice Swain Philbrick, Skowhegan
George Emil Ronne, Pawtucket, Rhode Island
Robert Somerville Borden, Bristol, New Brunswick, Canada
Douglas Willey Walker, Thomaston
Lester Ray Whitaker, Portsmouth, New Hampshire
Russell Wigh, Boston
Frederick F. Yonkman, Boston

THROUGH RECIPROCITY

Frederick Scarborough Gray, Portsmouth, New Hampshire
Allen Harold Knapp, Calais
Stanley Walter Machaj, Portsmouth, New Hampshire
James Calvin Martin, Baltimore
James Mitchell Parker, Chestnut Hill, Massachusetts
Arthur Gilson Pilch, Bloomfield, New Jersey
George Capron Poore, Philadelphia
Irvin Robert Schaen, Cincinnati

PREMEDICAL EDUCATION AT MIDDLESEX UNIVERSITY APPROVED

In response to the request of Middlesex University for approval of its Junior College for giving premedical education, the Approving Authority has given provisional approval for the school year, 1939–1940, and has so notified the institution. The decision was made after inspection of the buildings, facilities and equipment, interviews with members of the faculty, and an examination of the financial statements submitted. With the notification of approval, the Authority made certain recommendations, which it is reported the trustees are taking steps to carry into effect.

Under an act of 1936, amended in 1938, creating the Approving Authority, no candidate matriculating in a medical school after January 1, 1941, will be admitted to the examination for registration as a qualified physician if he has not had, before entering medical school, two years of premedical education in a college approved by the Approving Authority.

NOTE

The promotion of Dr. LeRoy A. Schall, instructor in laryngology at the Harvard Medical School, to the position of Walter Augustus Lecompte Professor of Otology and Professor of Laryngology, as of September 1, 1939, was recently announced at Harvard University. He succeeds Dr. Harris P. Mosher, who has become professor emeritus. Dr. Schall graduated from Jefferson Medical College in 1917. He has been on the staff of the Harvard Medical School since 1926, and on the staff of the Massachusetts Eye and Ear Infirmary since 1923, serving as surgeon in otolaryngology since 1935. He has also been assistant surgeon in laryngology at the Palmer Memorial Hospital since 1932.

CORRESPONDENCE

BIOGRAPHY OF DR. HARVEY CUSHING

To the Editor: Mrs. Cushing has requested me to prepare a biography of her husband and I should be most grateful to anyone who wishes to make letters, anecdotes or other memorabilia available.

Copies of all letters, no matter how brief, are desired, and if dates are omitted it is hoped that, when possible, these may be supplied (for example, from the postmark). If original letters or other documents are submitted, they will be copied and returned promptly.

A new medical library building is being erected at the Yale University School of Medicine to receive Dr. Cushing's library and collections, including his letters, diaries and manuscripts. Any of his friends who wish, now or later, to present correspondence, photographs or other memorabilia for permanent preservation among the Cushing papers will receive the appreciative thanks of the University.

JOHN F. FULTON, M.D.

333 Cedar Street,
New Haven, Connecticut.

THE MULTIPLE EPIDERMAL PUNCTURE TEST

To the Editor: I should like to call to the attention of your readers a skin-testing technic that I have been using for several years — the multiple epidermal puncture test. It is performed by placing the allergen on the skin and making about twelve microscopic punctures through the material directly into the epidermis. The test substance should cover an area about 3 mm. in diameter. The needle used for the punctures should be a solid one, as a perforated needle will obviously lead to test contamination.

The multiple epidermal puncture test is a simple one and once mastered can be performed rapidly. It gives uniform results and is very sensitive. Since the punctures are microscopic, trauma and bleeding are not produced and tell-tale test marks are not left on the skin. The test is not painful and for this reason is particularly useful in testing children. Furthermore, a large number of tests can be performed at one sitting.

ANGELO L. MAIETTA, M.D.

408 Main Street,
Winchester, Mass.

ERRATUM

In the paper "The Reciprocal Pharmacologic Effects of Amphetamine (Benzedrine) Sulfate and the Barbiturates," by Dr. Abraham Myerson, which was published in the October 12 issue of the *Journal*, the sentence beginning the fourth paragraph on page 561 should read:

> It is a synergist to atropine in all the physiologic effects of that drug,[4] or, conversely, atropine is a synergist to amphetamine sulfate because it blocks or inhibits the action of the parasympathetic nerves and allows the sympathetic effects of amphetamine sulfate to be more firmly established.

In editing the copy, a transposition was made so that the sentence, as published, implies that amphetamine sulfate acts on the parasympathetic nervous system. ED.

NOTICES

BOSTON GASTROENTEROLOGICAL SOCIETY

The next meeting of the Boston Gastroenterological Society will be held in the Dowling Amphitheater of the Boston City Hospital on Wednesday, November 8, at 12 o'clock noon.

Dr. Howard M. Clute will deliver an illustrated lecture on "Cancer of the Stomach."

PETER BENT BRIGHAM HOSPITAL

A joint medical and surgical clinic of the Peter Bent Brigham Hospital will be held on Wednesday afternoon, November 1, at 2:00. Drs. Elliott C. Cutler and Soma Weiss will speak on "Cough. Chest Pain." A clinicopathological conference, conducted by Dr. Elliott C. Cutler, will follow.

On Thursday morning, November 2, at 8:30, there will be at the Peter Bent Brigham Hospital a combined clinic, conducted by Dr. Soma Weiss, of the medical, surgical, orthopedic and pediatric services of the Children's Hospital and the Peter Bent Brigham Hospital.

Physicians and students are cordially invited to attend.

ELLIOTT C. CUTLER, M.D., *Secretary.*

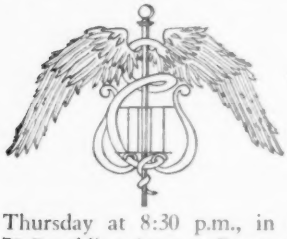
GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday evening, November 7, at 8:15.

Dr. Morris Fishbein, editor of the *Journal of the American Medical Association,* will speak on "American Medicine and the National Government."

DAVID B. STEARNS, M.D., *Secretary.*

BOSTON DOCTORS' SYMPHONY ORCHESTRA



The Boston Doctors' Symphony Orchestra will rehearse under Alexander Theide, former concertmaster with the Cleveland Symphony Orchestra and the Philadelphia Symphony Orchestra, every Thursday at 8:30 p.m., in Studio A, Station WMEX, 70 Brookline Avenue, Boston. Those interested in becoming members should communicate with Dr. Julius Loman, Pelham Hall Hotel, Brookline (BEA 2430).

FAULKNER HOSPITAL

The usual clinicopathological conference of the Faulkner Hospital will be held at the Faulkner Hospital on Thursday, November 2, at 5:00 p.m. There will be a discussion of cases by Drs. W. R. Ohler and E. L. Young, Jr.

All interested members of the medical profession are cordially invited to attend.

BOSTON INFECTIOUS DISEASE SOCIETY

The Boston Infectious Disease Society will meet in the Laboratory Study of the Children's Hospital on Thursday, November 2, at 4:30 p.m.

PROGRAM

Panleukopenia of Cats: A virus disease. Dr. W. Hammon.

Observations in the Role of Birds and Mosquitoes in the Spread of Equine Encephalomyelitis. Dr. W. A. Davis.

Experiments with *Haemophilus influenzae* (human) in Swine. Dr. John Mote.

LEROY D. FOTHERGILL, M.D., *Secretary.*

AMERICAN SANATORIUM ASSOCIATION

The sixteenth fall meeting of the Eastern Section of the American Sanatorium Association will be held at the Westfield State Sanatorium, Westfield, on November 3 and 4. Scientific sessions will be held on Friday afternoon and Saturday morning, and Friday evening there will be an x-ray conference in charge of Dr. F. Maurice McPhedran, of the Germantown Hospital, Philadelphia.

WILLIAM HARVEY SOCIETY

A meeting of the William Harvey Society of Tufts College Medical School will be held in the auditorium of the Beth Israel Hospital, Boston, on Friday, November 3, at 8:00 p.m. Dr. Shields Warren will speak on "The Effect of Radium and X-ray Irradiation on Tissues." The meeting will be conducted by Dr. H. E. MacMahon.

On Friday, December 8, Dr. Richard H. Overholt will address the society on the topic "Clinical Studies in Primary Carcinoma of the Lung." Dr. James Hepburn will act as chairman.

Members of the medical profession and their friends are cordially invited to attend.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS, UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	ORTHOPEDIC CONSULTANT
Haverhill	November 1	William T. Green
Lowell	November 3	Albert H. Brewster
Salem	November 6	Harold C. Bean
Brockton	November 9	George W. Van Gorder
Gardner	November 14	Mark H. Rogers
Northampton	November 15	Garry deN. Hough, Jr.
Worcester	November 17	John W. O'Meara
Pittsfield	November 20	Francis A. Slowick
Fall River	November 27	Eugene A. McCarthy
Hyannis	November 28	Paul L. Norton

AMERICAN ACADEMY OF DERMATOLOGY

About 600 leading dermatologists from all parts of the nation are expected to attend the second annual meeting of the American Academy of Dermatology and Syphilology at the Bellevue-Stratford Hotel, Philadelphia, November 6 to 8 inclusive. Sessions will be held in the form of symposiums, special lectures in "courses" lasting from one to four hours each, and numerous luncheon round-table discussions.

There will be over fifty lecturers on the three-day program including the guest speaker, Dr. Cornelius P. Rhoads, of the Rockefeller Institute, New York City, who will speak at 11 a.m., Monday, November 6, on "Vitamin B Complex." Among those on the program are Drs. John G. Downing and Jacob H. Swartz, of Boston, whose respective subjects are "Eczema (all forms)" and "The Treatment of Resistant Mycotic Infections with Ethyl Iodide Inhalations." Clinical presentations will take place at Jefferson Medical School, Philadelphia, all day Tuesday, November 7.

Registration begins at 5 p.m., Sunday, November 5, followed by meetings of the Membership Committee and the Board of Directors. The first executive session is set for 10 a.m., Monday, and in the evening, following special lectures and a luncheon round-table discussion, there will be a dinner meeting of the Board of Directors and a smoker. The annual banquet is set for 7 p.m., Tuesday. Four symposiums, concerning syphilis, allergy, pharmaceutical therapeutics, and the physiology and chemistry of the skin, are to be held Wednesday morning, November 8.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING MONDAY, OCTOBER 30

MONDAY, OCTOBER 30

*8:15 p.m. New England Heart Association. Boston Medical Library, 8 Fenway, Boston.

TUESDAY, OCTOBER 31

*9–10 a.m. "Measles." Professor Edwin B. Wilson. Joseph H. Pratt Diagnostic Hospital.

*10 a.m.–12:30 p.m. Boston Dispensary tumor clinic.

WEDNESDAY, NOVEMBER 1

*12 m. Clinicopathological conference. Children's Hospital Amphitheater.

*2 p.m. Joint medical and surgical clinic. Peter Bent Brigham Hospital.

THURSDAY, NOVEMBER 2

*8:30 a.m. Combined clinic of the medical, surgical, orthopedic and pediatric services of the Children's Hospital and the Peter Bent Brigham Hospital, at the Peter Bent Brigham Hospital.

4:30 p.m. Boston Infectious Disease Society. Laboratory Study of the Children's Hospital.

5 p.m. Faulkner Hospital, clinicopathological conference.

FRIDAY, NOVEMBER 3

*10 a.m.–12:30 p.m. Boston Dispensary tumor clinic.

12 m. Clinical meeting of the Children's Medical Service, Massachusetts General Hospital. Ether Dome.

*12 m. Urological conference at the Massachusetts General Hospital, lower amphitheater, Out-Patient Department.

*8 p.m. William Harvey Society. Auditorium of the Beth Israel Hospital.

SATURDAY, NOVEMBER 4

*10 a.m.–12 m. Medical staff rounds of the Peter Bent Brigham Hospital. Conducted by Dr. Soma Weiss.

*Open to the medical profession.

OCTOBER 27 — Massachusetts Italian Medical Society. Page 633, issue of October 19.

OCTOBER 30 — New England Heart Association. Page 589, issue of October 12.

OCTOBER 31 — Massachusetts General Hospital. Research meeting. Page 633, issue of October 19.

NOVEMBER 1 — Peter Bent Brigham Hospital. Joint medical and surgical clinic. Page 675.

NOVEMBER 2 — Combined clinic of the medical, surgical, orthopedic and pediatric services of the Children's Hospital and the Peter Bent Brigham Hospital. Page 676.

NOVEMBER 2 — Boston Infectious Disease Society. Page 676.

NOVEMBER 2 — Faulkner Hospital, clinicopathological conference. Page 676.

NOVEMBER 3 — William Harvey Society. Page 676.

NOVEMBER 3–4 — American Sanatorium Association. Page 676.

NOVEMBER 6–8 — American Academy of Dermatology. Page 676.

NOVEMBER 6–11 — New England Medical Center. Teaching Clinics on Cancer. Page 633, issue of October 19.

NOVEMBER 7 — Greater Boston Medical Society. Page 676.

NOVEMBER 8 — Boston Gastroenterological Society. Page 675.

NOVEMBER 8, 9 — New England Society of Physical Medicine, in conjunction with the Academy of Physical Medicine, Hotel Kenmore, Boston.

NOVEMBER 9 — Pentucket Association of Physicians. 8:30 p.m., Hotel Bartlett, Haverhill.

DECEMBER 2 — American Board of Obstetrics and Gynecology. Page 1019, issue of June 15.

DECEMBER 8 — William Harvey Society. Page 676.

JANUARY 6, JUNE 8–11, 1940 — American Board of Obstetrics and Gynecology. Page 160, issue of July 27.

JANUARY 22–25, 1940 — American Academy of Orthopaedic Surgeons. Hotel Statler, Boston.

MARCH 7–9, 1940 — The New England Hospital Association. Hotel Statler, Boston.

MAY 14, 1940 — Pharmacopoeial Convention. Page 894, issue of May 25.

JUNE 7–9, 1940 — American Board of Obstetrics and Gynecology. Page 1019, issue of June 15.

DISTRICT MEDICAL SOCIETY

SUFFOLK

NOVEMBER 2 — Censors' meeting. Page 441, issue of September 14.

NOVEMBER 29 — Scientific meeting. Treatment of Syphilis. Dr. Harold T. Hyman, Dr. Louis Chargin, and Dr. William Leifer, of New York City.

JANUARY 31, 1940 — Scientific meeting. Subject to be announced later.

MARCH 27 — Scientific meeting. Symposium on Ulcerative Colitis and Diarrheas. Under the direction of Dr. Chester M. Jones.

APRIL 24 — Annual meeting in conjunction with the Boston Medical Library. Election of officers. Program and speakers to be announced later.

BOOKS RECEIVED FOR REVIEW

Sketches in Psychosomatic Medicine. Nervous and Mental Disease Monograph. No. 65. Smith E. Jelliffe. 155 pp. New York: Nervous and Mental Disease Publishing Company, 1939. $3.00.

The Neurogenic Bladder. Frederick C. McLellan. 206 pp. Springfield, Illinois, and Baltimore: Charles C Thomas, 1939. $4.00.

Circulatory Diseases of the Extremities. John Homans. 330 pp. New York: The Macmillan Co., 1939. $4.50.

Synopsis of Pediatrics. John Zahorsky and T. S. Zahorsky. Third edition. 430 pp. St. Louis: C. V. Mosby Co., 1939. $4.00.

A Synopsis of Surgical Anatomy. Alexander L. McGregor. Fourth edition. 664 pp. Baltimore: William Wood & Co., 1939. $6.00.

Handbook of Bacteriology: For students and practitioners of medicine. Joseph W. Bigger. Fifth edition. 466 pp. Baltimore: William Wood & Co., 1939. $4.25.

Pictorial Midwifery: An atlas of midwifery for pupil midwives. Comyns Berkeley. Third edition. 166 pp. Baltimore: William Wood & Co., 1939. $3.00.

Treatment of Some Common Diseases: Medical and surgical. By various authors. Edited by T. Rowland Hill. 398 pp. Baltimore: William Wood & Co., 1939. $5.00.

The Dysenteric Disorders: The diagnosis and treatment of dysentery, sprue, colitis and other diarrhoeas in general practice. Philip Manson-Bahr. 613 pp. Baltimore: William Wood & Co., 1939. $8.00.

Physiological Chemistry: A text-book for students. Albert P. Mathews. Sixth edition. 1488 pp. Baltimore: William Wood & Co., 1939. $8.00.

Caesarean Section: Lower segment operation. C. McIntosh Marshall. 230 pp. Baltimore: William Wood & Co., 1939. $6.50.

A History of Tropical Medicine: Based on the Fitzpatrick lectures. H. Harold Scott. 2 vol. 1165 pp. Baltimore: William Wood & Co., 1939. $12.50 per set.

Stedman's Practical Medical Dictionary. Thomas L. Stedman and Stanley T. Garber. Fourteenth revised edition. 1303 pp. Baltimore: William Wood & Co., 1939. $7.50.

Obstetrical Practice. Alfred C. Beck. Second edition. 858 pp. Baltimore: Williams & Wilkins Co., 1939. $7.00.

BOOK REVIEWS

Doctors, Nurses and Dickens. Robert D. Neely. 153 pp. Boston: The Christopher Publishing House, 1939. $1.50.

This is one of the most entertaining and delightful books that has come into the reviewer's hands. The author has selected those passages from Dickens's books which treat of medicine, the doctor and his variety of assistants, such as nurses, interns, students and finally undertakers. It was necessary to include them all in order to get a complete picture. Furthermore, the title is sufficiently indefinite to permit considerable rambling on the part of the author. It is not only a pleasant intermezzo of medicine as studied by Dickens in relation to all strata of society but a delightful picture of Dickens's own life, troubles and vicissitudes. To one who reads the book it will give not only a most pleasant and warm evening but

considerable food for thought. For instance, the sayings of Esther Summerson, the heroine of *Bleak House*, after her marriage to Dr. Allan Woodcourt, show in what high regard Dickens held the medical profession. She says: "I never walk out with my husband, but I hear the people bless him. I never go into a house of any degree, but I hear his praises, or see them in grateful eyes. I never lie down at night, but I know that in the course of that day he has alleviated pain, and soothed some fellow-creature in the time of need. I know that from the beds of those who were past recovery, thanks have often, often gone up in the last hour, for his patient ministration. Is not this to be rich?"

It must be remembered that Dickens did satirize human life, but he did not do so to degrade it. He did not wish to pull down what was high into the neighborhood of what was low. He really satirized only the selfish and the hard-hearted and the cruel; he expressed in hideous light the principle which when acted on gives a power to man in the lowest grades to carry on a more terrific tyranny than if placed on thrones. The physician who gave of the milk of human kindness was treated with respect. On the other hand, he ridiculed the physician who with scientific outlook neglected his patient or those who gave lengthy scientific reports leading to nowhere. This is best shown by Dickens's characterization of the Mudfog Medical Association held in the town of Mudfog.

The carefully written text produced such an enthusiasm in the reviewer that he cannot help but recommend it to all and sundry.

Cancer Handbook of the Tumor Clinic, Stanford University School of Medicine. Edited by Eric Liljencrantz. 114 pp. Stanford University: Stanford University Press, 1939. $3.00.

This handbook is based on postgraduate instruction in the diagnosis and treatment of malignant tumors given at Stanford University School of Medicine. It is in brief syllabus form and attempts to cover only the more frequent forms of the disease. Several useful diagrams are presented.

The diagram on page 3 regarding intrinsic and extrinsic factors in etiology might well be omitted. On page 5 an interesting family tree is presented showing three generations with a high incidence of carcinoma, particularly carcinoma of the breast. The reviewer questions the accuracy of bilateral breast cancer's occurring as frequently as the diagram would imply, since involvement in the second breast is usually the result of metastasis or extension from that first involved rather than true primary bilateral tumor.

The brief chapter on "Principles of Radiation Therapy" is simple and straightforward. Cancers of the skin, eye and lip, of the oropharynx and neck, of the gastrointestinal tract, of the lung and of the breast are treated in brief chapters as are gynecological and genitourinary cancers, the leukemias and lymphoblastomas, tumors of the central nervous system and bone tumors. A brief bibliography is appended that deals primarily with recently published work. There are several excellent photographs of lesions of the skin.

In the treatment of cancer of the breast, operation is recommended in Stage I, and preoperative radiation or radiation without operation in Stage II. In Stage III roentgen castration is mentioned as an adjunct to treatment in cases in which cancer has occurred before the menopause.

In the discussion of carcinoma of the cervix a combination of radium and x-ray therapy is recommended in all except Stage I, where radium alone is advised.

The section on genitourinary cancer consists of five brief subdivisions, no one of which is sufficiently amplified to present any information of value.

This handbook would be of definite value for the third- or fourth-year student desiring a brief compendium of the important types of cancer, but falls short of giving sufficient information to be of value to the practitioner whose experience with malignant disease has been limited.

Syphilis, Gonorrhea and the Public Health. Nels A. Nelson and Gladys L. Crain. 359 pp. New York: The Macmillan Co., 1938. $3.00.

The point of view of the authors of this book is definitely that of the public-health officer, and it is written in simple straightforward language so as to be useful to the physician, social worker, nurse and such lay persons as are interested in the public-health aspects of the problem.

The first part of the book gives general information about genitoinfectious diseases and their incidence, prevalence, distribution and mortality. The rest of the book takes up control measures, costs, social-hygiene considerations and what has been accomplished in Scandinavian countries.

The absurdity of many of the laws is humorously and effectively discussed, and the futility of merely "passing a law about it" is well shown. The authors recommend simple and flexible laws, which merely provide a background for sensible control measures. They add that it is useless to try to legislate good medicine without first providing good training for those who should carry out the treatment of the patients and the necessary control measures and that the laws should not control the physicians and health officers but be designed to be tools in their hands in order to be most effective.

Throughout the book the note is frequently sounded of helpfulness to the practitioner. That so much emphasis should be placed on this point is not surprising, since those who know Dr. Nelson and his work realize that he has always conspicuously conducted his department along this line. Any physician who fears interference from his state board of health should read the book with care, for the advisability of help and service to the practitioner is constantly reiterated.

Treatment in General Medicine. Edited by Hobart A. Reimann. 3 vol. 2834 pp. Desk index, 107 pp. Philadelphia: F. A. Davis Co., 1939. $30.00.

This three-volume system on treatment in general medicine should prove valuable to the general practitioner. It is a complete source of information on all possible therapeutic procedures that come up in practice. In addition to the general topics considered in the average textbook on treatment, this work emphasizes psychotherapy and physiotherapy in their manifold applications, including occupational therapy and irradiation. There are also sections on minor surgical, gynecological and obstetric treatment, and on the care of the aged and of patients with cancer.

The work is a collaboration by thirty-four eminent American physicians, each an expert in his field. The volumes are well illustrated and substantially bound, and the print is excellent. There is a thorough index.